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VOLUME 40 AUGUST 1944 NUMBER 2

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LABYRINTHITIS DUE TO PNEUMOCOCCUS TYPE III

HISTOPATHOLOGIC STUDIES

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AND

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NEW YORK

The frequent complications arising from acute otitis caused by Pneumococcus type III and the difficulties of their diagnosis and treatment are well known to the otologist. The aim of this paper is to throw additional light on the peculiarities of these complications, particularly those of labyrinthitis. Histologic examination of cases with fatal ending shows a certain uniformity of the pathologic process, and this indicates some degree of regularity in the pathogenesis. Recognition of this regularity may help to prevent the development of the complications which frequently lead to severe functional damage of the ear or even to the death of the patient.

Middle ear infections caused by Pneumococcus type III are rather frequent. In 15 to 20 per cent of the cases of acute otitis media which come to operation, the disease is caused by this germ.

We report 5 cases of mastoiditis due to Pneumococcus type III. In 3 diffuse labyrinthitis developed and, subsequent to this, meningitis; in 2 the meningitis was from other sources. In the latter 2 cases an infection of the labyrinth was not shown, but certain features were manifest which are important for the understanding of the genesis of labyrinthitis. Cases 1, 4 and 5 were observed in the department of otolaryngology of the Presbyterian Hospital in New York and cases 2 and 3 were observed in the General Hospital in Vienna, Austria.

CASE 1

History.—F. T., a man 28 years of age, was admitted to the Presbyterian Hospital in New York on Jan. 29, 1936. He first began to have a discharging right ear twenty years before. The ear discharged intermittently for about ten years. Following that period it was dry for ten years. Two and a half months before admission to the hospital the ear began to discharge again, and there was some associated pain over the mastoid process and the right side of the head. A week before admission the patient complained of some headache over the right eye. On the morning of admission severe dizziness and vomiting developed. This condition persisted all day and became worse on movement.

Physical Examination.—The temperature was 98.6 F.; the pulse rate, 100; the respiratory rate, 20; the blood pressure, 120 systolic and 80 diastolic. The left drum was slightly thickened in its posterior quadrant. The right ear showed thin yellowish bloody pus in the external canal. The drum membrane was thickened and red and showed a perforation in the posterior part. Over the mastoid process there was slight diffuse tenderness. Rests of hearing were present in the right ear; there was spontaneous nystagmus of 1 degree to the left, with past pointing to the right.

Course.—On the following day the patient's temperature rose to 101 F. and radical mastoidectomy was performed. The mastoid process was moderately well pneumatized. A small amount of pus under pressure was released from the antrum. There was an area of soft bone extending from the aditus ad antrum toward the epibulbar-retrofacial region. The lateral sinus and dural plate looked normal. No involvement of the semicircular canals could be seen. Culture of material taken at the operation showed Pneumococcus type III.

A second operation was done the following day because of the development of signs and symptoms of generalized meningitis. The sigmoid sinus and the dura of the middle and the posterior fossa were exposed and the dura incised. The patient died the day after the second operation. Autopsy showed acute cerebrospinal leptomeningitis due to Pneumococcus type III.

Histologic Examination of the Temporal Bones (horizontal serial sections).[1]—(*a*) Right middle ear: The ossicles with the exception of the stapes were absent. The footplate of the stapes was covered with a large mass of connective tissue which filled the niche of the oval window. The mucosa of the middle ear was thick, rich in fibrils and infiltrated with round cells and polymorphonuclear leukocytes. There were masses of red and white blood cells and fibrin in the middle ear cavity. The niche of the round window was filled with edematous and infiltrated connective tissue. The mucosa of the

The authors were assisted by grants from the Research Council of the American Otological Society and the Hayden-Coakley Fund.

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1. The histologic observations in this case were briefly mentioned by E. P. Fowler Jr. and P. C. Swenson (Petrositis: A Roentgenologic and Pathologic Correlation, Am. J. Roentgenol. **41**:317, 1939).

eustachian tube was free from inflammatory changes. The petrous tip was diploic; the marrow spaces were filled with fat and hemopoietic marrow.

(*b*) Right mastoid process: The mastoid bone showed a big operative cavity. A few perilabyrinthine pneumatic cells were left. They were small and contained edematous and moderately infiltrated mucosa. In the part of the posterior fossa (fig. 1). The abscess measured 12 to 15 mm. in length and 5 to 7 mm. in width; it extended forward into the posterior wall and the roof of the internal auditory meatus. The abscess cavity was filled with polymorphonuclear leukocytes and fibrin. The walls were formed by granulation tissue which covered the underlying bone and dura. In

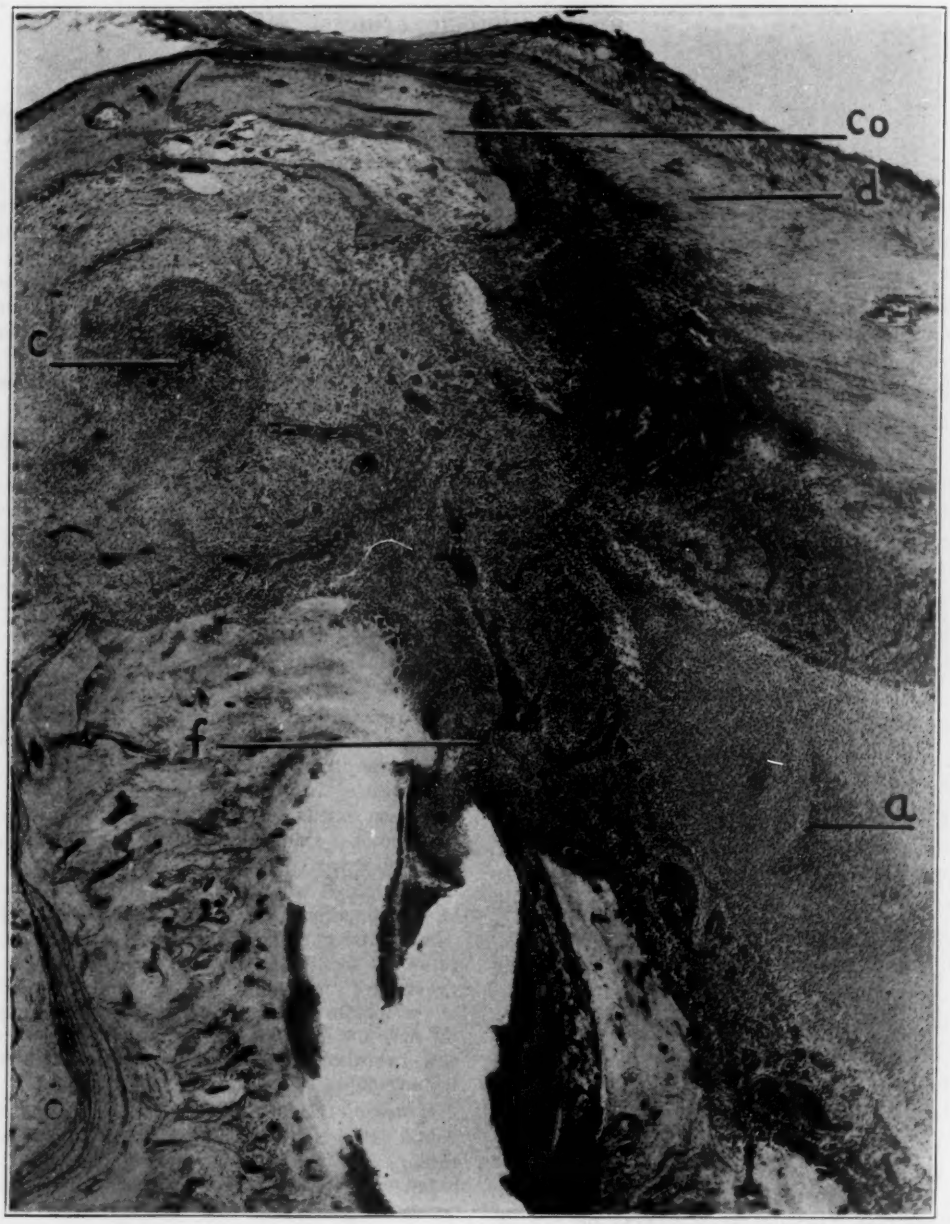

Fig. 1 (case 1).—Horizontal section showing the deep abscess of the posterior fossa, the epidural abscess and the perforation into the superior vertical canal with subsequent diffuse purulent labyrinthitis. *a* indicates the abscess cavity; *c*, the infected cell in the sinodural angle; *co*, the cortex of the posterior fossa, being destroyed by osteoclasts; *d*, the infiltrated dura of the posterior fossa; *f*, the fistula into the superior vertical canal with progressive osteoclastic destruction of the adjacent parts of the labyrinthine capsule.

cells in the anterior part of the sinodural angle there was marked purulent inflammation of the mucosa and osteoclastic breakdown of the intercellular septums. This area of destruction extended along the cells at the petrous ridge into a big epidural abscess of the upper

the posterior part of the abscess (fig. 2) there were vivid osteoclastic destruction of the bony walls and progressive rarefying osteitis of the adjacent parts of the labyrinthine capsule (fig. 3). In the anterior half new formation of weblike fibril bone in a netlike

arrangement was prevalent. In two places the abscess had broken through anteriorly into the superior vertical canal (fig. 1), into the lower portion of the lean end and into the highest part of the convexity. The dura showed leukocytic infiltration of its outer layers; its inner layers were intact.

(*c*) Right inner ear: The scala tympani and the scala vestibuli were filled with purulent exudate. Reissner's membrane was destroyed. The basilar membrane showed marked leukocytic infiltration. Corti's organ was recognizable only in the basal coil. The membrane of the round window was infiltrated with leukocytes. The cochlear aqueduct was filled in its peripheral wider part with purulent exudate. Near the cochlear opening the duct was filled with a network of loose connective tissue which was infiltrated with leukocytes and contained a few calcified concretions.

(*d*) Right vestibule and semicircular canals: The perilymphatic spaces were filled with hemorrhagico-purulent exudate. The membranous parts were still recognizable and contained a moderate amount of exudate. The walls were infiltrated with leukocytes. The maculae acusticae were still recognizable in some sections; the cristae ampullares were somewhat better preserved (fig. 4). The endolymphatic duct and sac contained a moderate amount of purulent exudate. The annular ligament of the stapes was partially destroyed and heavily infiltrated with leukocytes. In some sections, the footplate was separated from the annular ligament both anteriorly and posteriorly, and the resultant gaps were filled with leukocytes and red blood cells.

(*e*) Right internal auditory meatus: The canals of the nerves and vessels which lead into the cochlea and the vestibule were filled with leukocytes. There was purulent exudate in the fundus, as well as leukocytic infiltration between the fibers of the eighth nerve.

(*f*) Left middle ear: The niche of the round window contained some purulent exudate, and its mucosa was infiltrated with leukocytes. There was also leukocytic infiltration of the mucosal lining of the stapedial footplate. The mastoid process was well pneumatized and without pathologic changes.

(*g*) Left inner ear: Fresh seropurulent meningogenic labyrinthitis was observed. There was leukocytic infiltration of the membrane of the round window and of the annular ligament of the stapes.

(*h*) Left internal auditory meatus: There was purulent exudate in the meatus. The eighth nerve showed moderate leukocytic infiltration. All canals of the labyrinthine vessels and nerves were filled with leukocytes, and this exudate could be traced into the labyrinthine cavities. There were no major changes in the spiral ganglion.

Summary.—A 28 year old patient had recurrent right-sided middle ear infections for twenty years. The last infection started two and a half months before hospitalization and produced few symptoms throughout the time; however, labyrinthine meningitis suddenly developed, and the patient died within four days.

Histologic examination showed that from infected cells in the anterior part of the sinodural angle an epidural abscess of the posterior fossa had developed which by an anterior approach had broken into the superior vertical canal in two places, causing purulent labyrinthitis. The labyrinthitis spread through the internal auditory meatus to the leptomeninges. The left ear showed meningogenic seropurulent labyrinthitis.

Fig. 2 (case 1).—Horizontal section showing the deep abscess of the posterior fossa. *a* indicates the anterior part with a network of newly formed weblike fibril bone; *p*, the posterior part with vivid osteoclastic destruction.

CASE 2

History.—A. Z., a woman 66 years old, was admitted to the General Hospital in Vienna on March 9, 1929. Six weeks prior to this she experienced pain in the

right ear with tinnitus; the pain lasted three weeks; after that there was discharge from the ear with decrease of the pain. During the last four weeks the hearing had deteriorated. During the last week the patient complained of rotatory dizziness, and in the last three days she had frequent attacks of vomiting.

Physical Examination.—The temperature was 99.1 F.; the pulse rate, 82. There was spontaneous horizontal rotatory nystagmus of sceond degree to the left. Meningeal signs were not present. Tenderness was noted over the tip of the right mastoid process, with mucopurulent exudate in the external canal and sagging of the posterosuperior wall of the canal. The drum membrane was red and presented no landmarks. Perforation was not visualized. The left ear appeared normal. There was complete deafness in the right ear. On irrigation of this ear with water heated to 110 F. the spontaneous nystagmus disappeared.

Course.—March 9 simple mastoidectomy was done. The mastoid bone was well pneumatized. The cells were filled with granulations. A big retrolabyrinthine cell filled with pus was opened. Culture of material from the mastoid cells showed Pneumococcus type III. The labyrinthine signs disappeared, and the postoperative course was uneventful until March 31. At that time the external canal was dry and the retroauricular wound almost closed. On March 31 there was a sudden rise in temperature to 103 F. with nausea; soon the patient lost consciousness. A spinal tap showed cloudy cerebrospinal fluid. A few hours later the patient died. Culture of the spinal fluid revealed Pneumococcus type III. At autopsy diffuse purulent leptomeningitis was observed.

Histologic Examination of the Right Temporal Bone (serial sections).—(*a*) Middle ear: The mucous membrane was moderately thick and fibrillar, with perivascular round cell infiltration but without signs of acute inflammation. In the region of the windows, in the epitympanum and the hypotympanum there were bands and folds of organized tissue with cyst formation (fig. 5). The contents of the middle ear showed no pathologic change. The peritubal cells were well developed.

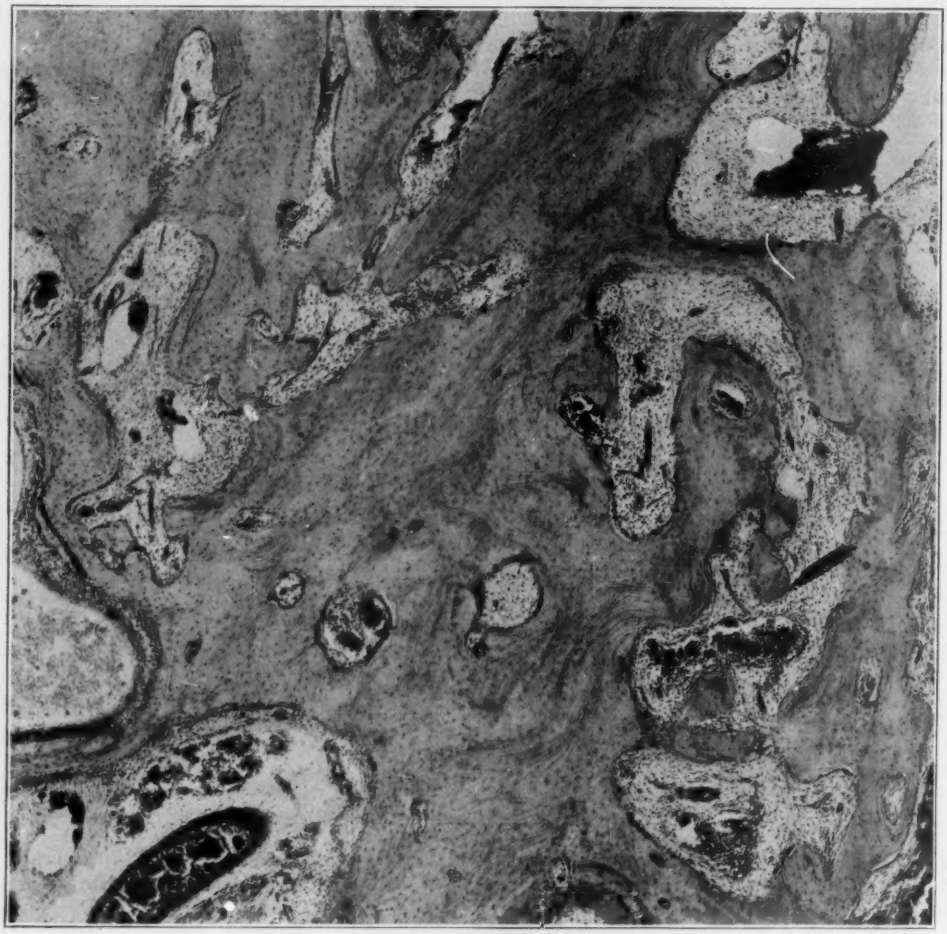

Fig. 3 (case 1).—Horizontal section showing rarefying osteitis of the labyrinthine capsule.

(*b*) Mastoid process: Most of the cells of the mastoid process were removed. Excepted were the perilabyrinthine cells, which surround the labyrinthine capsule on all sides. The cells were largely lined by hyperplastic mucosa, which showed fibrosis in some areas and edema and round cell infiltration in others. Some of the lumens contained purulent exudate. The perivascular and marrow spaces of the intercellular septums and particularly those of the adjacent parts of the labyrinthine capsule showed extensive osteoclastic destruction of the walls with confluence of numerous

spaces into larger cavities. In some of them the walls were covered with a layer of osteoid or a network of newly formed weblike fibril bone; in others new formation of bone and osteoclastic destruction were simultaneously present. By way of this rarefying ("granulating") osteitis, large areas of the periosteal as well as of the enchondral capsule were being destroyed. The osseous wall of the lateral semicircular canal had been perforated in several places, and the infection had spread into the labyrinthine cavities. The well developed

(*c*) Labyrinth: The perilymphatic and endolymphatic spaces were filled with purulent exudate and necrotic masses. The membranous labyrinth was almost completely destroyed. Only in the basal turn of the cochlea were Reissner's membrane and a few remnants of Corti's organ still recognizable. The endosteum was intact,

Fig. 4 (case 1).—Horizontal section showing the ampulla of the posterior vertical canal. *c a* indicates the crista ampullaris; *e s*, the endolymphatic space; *p s*, the perilymphatic space.

retrolabyrinthine cells, which were only incompletely removed at the operation, led into a large epidural abscess of the posterior fossa, which extended forward into the vicinity of the internal auditory meatus. The abscess cavity was filled with purulent exudate; its walls were lined with granulation tissue; the rarefying osteitis was particularly marked in the vicinity of the cavity; the osseous wall of the convexity of the posterior vertical canal was destroyed in several places, and the abscess had perforated into the lumen. In the vicinity of the endolymphatic sac, all the layers of the dura were densely infiltrated with polymorphonuclear leukocytes, and its inner surface was covered with fibrinopurulent exudate.

with the exception of the area where the perilabyrinthine suppuration had broken into the lumens of the canals. In addition, in a few places in the semicircular canals some osteoclastic destruction originating from the inner surface was visible.

In the oval window the annular ligament was destroyed by a suppuration which extended from the vestibule into the middle ear (fig. 5). The footplate of the stapes was slightly dislocated toward the middle ear, but it was still covered on its outer surface by a

layer of the mucosa of the middle ear. The latter and the mucosal folds which surrounded the crura of the stapes showed some polymorphonuclear infiltration, which decreased in intensity toward the middle ear. The membrane of the round window was completely destroyed, and the round window was filled with a plug of granulation tissue which extended into the lowest part of the scala tympani. The endolymphatic duct and sac contained some purulent exudate. The cochlear aqueduct was patent and contained near its inner opening a large amount of purulent exudate. Toward the external opening of the duct the amount of exudate decreased.

(*d*) Internal auditory meatus: The vascular and nerve channels of the modiolus and of the vestibule were filled with polymorphonuclear leukocytes which led into a large abscess located in the fundus of the internal auditory meatus. There was purulent infiltration of the acoustic nerve and infiltration of the epineurial sheath of the facial nerve. Toward the meninges the abscess was walled off by a thick layer of granulation tissue, but this demarcation was not complete and the purulent infiltration extended from here along the inner surface of the meatus toward the posterior fossa.

Summary.—In a 66 year old patient with acute purulent otitis media and mastoiditis of six weeks' duration signs of serous labyrinthitis developed. Simple mastoidectomy was performed, and a well pneumatized mastoid process filled with granulations was found; a large retrolabyrinthine cell filled with pus was opened. Three weeks later, after an uneventful postoperative course, signs of purulent meningitis suddenly developed, and the patient died a few hours later.

Histologic examination showed that from the incompletely drained retrolabyrinthine cells a large epidural abscess had formed which broke through the posterior vertical canal into the labyrinth and led to purulent labyrinthitis, to formation of an abscess in the fundus of the internal auditory meatus and to subsequent meningitis. In addition the infection spread to the leptomeninges directly through the dura of the posterior fossa. From other diseased perilabyrinthine cells rarefying osteitis of the labyrinthine capsule had developed, which eroded the lateral semicircular canal.

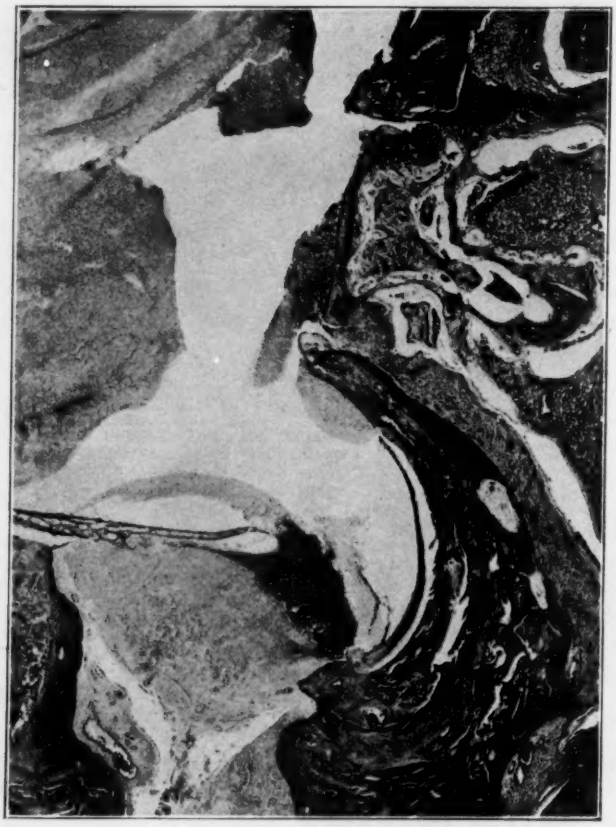

Fig. 5 (case 2).—Vertical section through the region of the windows. The stapes is embedded in cystic tissue; the annular ligament is completely destroyed, but the covering mucosa is intact. The membrane of the round window is destroyed and replaced by granulation tissue which extends into the scala tympani.

CASE 3

History.—J. F., a man aged 63, was admitted to the General Hospital in Vienna, Austria, on June 29, 1927. In the second half of March 1927 pain in the right ear was followed by discharge for seven weeks. On May 10 an attack of dizziness occurred, and the patient was admitted to the hospital. At that time no nystagmus or fistular symptom was present; the hearing was greatly reduced but not completely lost. Simple mastoidectomy was performed on May 14. A well pneumatized mastoid process was found; the cells were filled with granulations; those in the tip contained free pus. Culture of material taken from the mastoid cells

showed Pneumococcus type III. The postoperative course was uneventful, and the patient was discharged on June 13. The retroauricular wound was closed, the external canal was dry and the hearing was greatly improved. On June 28 (six weeks after operation) the patient noticed pain in the ear operated on, some secretion through the retroauricular scar and rapid deterioration of hearing, together with marked tinnitus, dizziness, vomiting and right-sided headaches.

Physical Examination.—The temperature was 98.4 F.; the pulse rate, 80, The sensorium was free from abnormality; there were no signs of meningeal irritation. The retroauricular wound on the right side was closed with exception of the lowest part; there was sagging of the posterosuperior wall of the external canal. The drum membrane was grayish-reddish, thickened and without clearly visible landmarks. The left ear showed a large dry central perforation of the drum membrane. The right ear was completely deaf and the caloric response completely lost. There was spontaneous horizontal rotatory nystagmus of 3 degrees to the left, with past pointing and falling to the right.

The next two days the condition remained the same. On July 1 the temperature rose to 99.5 F. There were still no signs of meningeal irritation. Operation on the labyrinth was decided on, but the patient died at the beginning of the induction of anesthesia. Autopsy showed purulent basal leptomeningitis.

Histologic Examination of the Right Temporal Bone (vertical serial sections).—(*a*) Middle ear and antrum: A moderately thick and fibrillar mucosa was seen with some perivascular round cells and plasma cell infiltration. The attic contained masses of organized connective tissue with cyst formation in which the head of the malleus and the body of the incus were embedded. Similar tissue masses with formation of cystic cavities were found in the hypotympanum and particularly in the region of the oval and round windows. Here the cysts contained purulent exudate, and the mucosa showed a predominantly polymorphonuclear infiltration which toward the windows increased in intensity.

(*b*) Eustachian tube: There was slight catarrhal inflammation of the mucosa. Good development of the peritubal cells was noted. The majority showed thick mucosa. Some of the cells contained purulent exudate; others were filled with loose, rather cellular connective tissue. In the peripheral parts of these cells new formation of trabeculae of weblike fibril bone was noted. The rest of the petrosal tip consisted of diploic bone with fat cells and hemopoietic tissue in the marrow spaces.

(*c*) Mastoid process: There was a large operative defect, which was partially filled with a mass of tissue. This consisted of a superficial layer of granulation tissue and a deeper layer of edematous, well vascularized fibrillar connective tissue, in the deeper parts of which was a network of newly formed trabeculae of weblike fibril bone. There had been incomplete operative removal of the pneumatic cells. In particular the deep cells of the tip, the retrofacial infralabyrinthine cells, the retrolabyrinthine cells and groups of cells in the sinodural angle had not been drained. These cells were filled partly with purulent exudate and partly with organized tissue, which frequently contained trabeculae of newly formed weblike fibril bone. The retrofacial-epibulbar-infralabyrinthine cells had been transformed, after destruction of most of the intercellular septums, into a big cavity lined by granulation tissue and containing purulent exudate. The abscess cavity surrounded the posteroinferior part of the labyrinth capsule and extended to the dura of the posterior fossa, which was exposed in a large area. From here an epidural abscess could be traced along the posterior surface of the petrous bone forward into the upper wall of the internal auditory meatus, upward to the dura of the middle fossa and downward toward the bulb of the jugular vein, which was reached in one place. The posterior surface of the labyrinthine capsule was eroded, the adjacent areas of the bone showed progressive rarefying osteitis, and the abscess had broken through into the lean end of the posterior semicircular canal.

(*d*) Inner ear: Both scalae of the cochlea, the vestibule and the semicircular canals contained purulent exudate. Reissner's membrane and Corti's organ were completely destroyed. The purulent exudate which filled the lowest part of the scala tympani pushed the membrane of the round window outward toward the niche. The central part of the membrane was densely infiltrated with polymorphonuclear leukocytes, and the infiltration extended with gradually decreasing intensity into the mucosal covering of the membrane and into the walls of the cystlike cavities.

The cochlear aqueduct was patent in its entire length and filled with leukocytes and red blood cells.

The utricle and the saccule were completely destroyed. The ampulla of the posterior vertical canal was still recognizable; the rest of the membranous semicircular canals was destroyed.

The annular ligament of the stapes was preserved only in its posteroinferior quadrant and was densely infiltrated with leukocytes. The rest was destroyed, but there was no marked dislocation of the stapes. The purulent masses which filled the vestibule extended into the gap which resulted from the destruction of the annular ligament and beyond that into the mucosal layer which covered the footplate and the walls of the niche of the oval window.

The endolymphatic duct contained pus. The endolymphatic sac lay within the epidural abscess described, but its walls were intact. The lumen contained a few leukocytes.

There was marked leukocytic infiltration of the vascular and nerve channels of the modiolus and the vestibule, which could be followed into the fundus of the internal auditory meatus. There an accumulation of purulent and hemorrhagic exudate was present; from here the purulent infiltration continued toward the meninges. The eighth nerve showed in the fundus of the meatus a leukocytic infiltration of the epineurial and perineurial connective tissue.

Summary.—A 63 year old patient with acute otitis media and mastoiditis was operated on when after seven weeks serous labyrinthitis developed. Six weeks later, after an uneventful postoperative course, the patient suddenly presented signs of diffuse purulent labyrinthitis and died after three days without showing any meningeal signs.

Histologic examination disclosed that in the insufficiently drained retrofacial cells a large abscess had originated which extended to the posterior fossa and led to the formation of a large epidural abscess. This abscess had eroded the lean end of the posterior vertical canal and had broken into the labyrinth causing purulent, necrotizing labyrinthitis with subsequent leptomeningitis.

In the cases described to this point a deep abscess of the posterior fossa led to an infection of the labyrinth by breaking into one of the

semicircular canals. Relatively frequently, however, the infection progresses through the dura of the posterior fossa to the leptomeninges without affecting the labyrinth. This is seen in the following 2 cases.

CASE 4

History.—H. A., a man of 45 years, was admitted to the Presbyterian Hospital on June 27, 1935. In the second half of April 1935 he began to complain of earache and ringing in the left ear. Myringotomy was performed on this ear the next morning. He still complained of pain and had some discharge, slight fever and a few chills. All the symptoms disappeared within a few days, and he felt well until June 26, when he noticed a peculiar feeling of obstruction in the left ear. The next morning a terrific headache developed with repeated attacks of vomiting. By noon he was delirious and incontinent and suffered many chills.

Physical Examination.—The patient was semistuporous with marked meningeal signs. The spinal fluid was cloudy and contained 4,040 cells. Culture revealed Pneumococcus type III in pure culture. The drum membranes appeared normal.

Course.—The condition became rapidly worse, and the patient died forty hours after admission. Autopsy showed diffuse purulent leptomeningitis.

Histologic Examination of the Temporal Bones (horizontal serial sections).—(*a*) Left middle ear: The mucosa was rich in fibrillar tissue and showed the picture of "hyperplasia" and, in addition, in some places polymorphonuclear leukocytes in its superficial layers. The lumen contained a small amount of seropurulent exudate. The ossicles showed no pathologic change. The antrum was wide, and its lumen was filled with a big plug of organized tissue which was connected with the walls of the antrum by numerous tissue bridges (fig. 6). The mucosa of the eustachian tube was normal. The pericarotid cells were moderately well developed and were lined with hyperplastic mucosa. The rest of the petrous tip contained marrow spaces which were almost entirely filled with fat marrow. The marrow spaces in the neighborhood of the pericarotid cells showed edema and some proliferation of the perivascular cell elements. In some marrow spaces the fat marrow showed extensive transformation into fine fibrillar marrow, in which a network of weblike fibril bone was formed. There was also apposition of some osteoid to the walls.

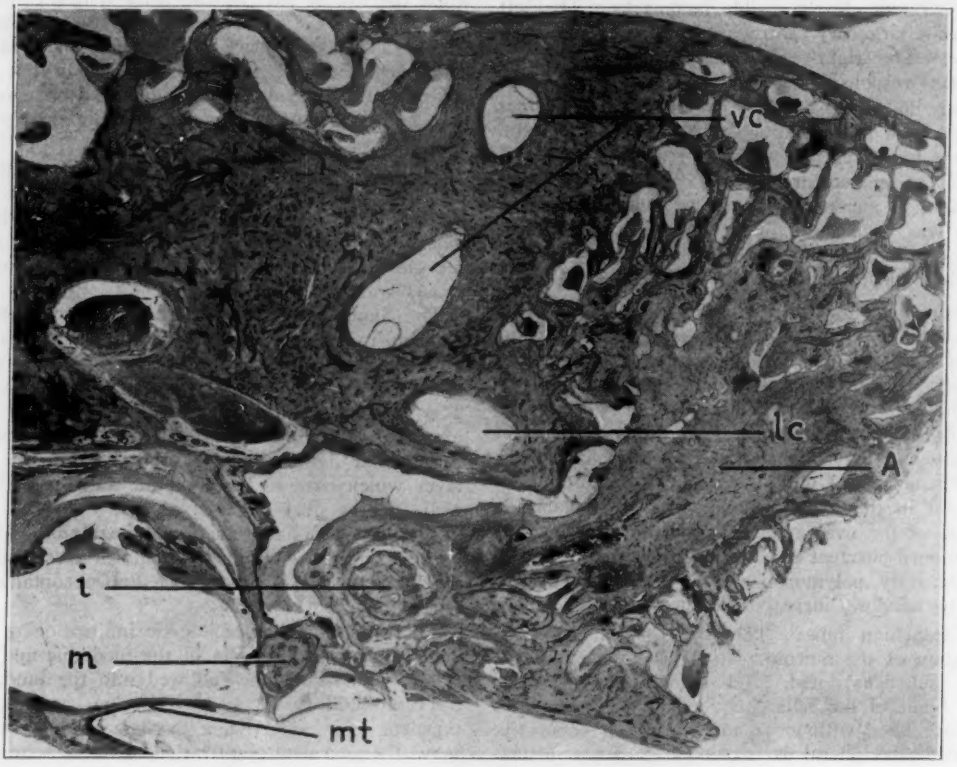

Fig. 6 (case 4).—Horizontal sections. *A* indicates the antrum filled with a big plug of organization tissue; *v c*, the superior vertical canal; *l c*, the lateral canal; *i*, the incus embedded in organization tissue; *m*, the malleus with the tendon of the tensor tympani muscle; *m t* the membrana tympani.

(*b*) Left mastoid process: The bone was well pneumatized; most of the cells contained a greatly thickened fibrillar mucosa which was heavily infiltrated with lymphocytes and plasma cells (fig. 7). In some places there was a moderate amount of polymorphonuclear leukocytes. In some of the cells organization tissue with formation of cystic cavities was noticed. The walls of many cells were lined with a thin layer of newly formed osteoid. The perilabyrinthine cells were well developed and showed the same characteristics as the rest of the pneumatic system; they extended above and behind the labyrinth into the immediate neighborhood of the internal auditory meatus. The cells which were located close to the internal auditory

meatus were lined with a relatively thin mucosa without any sign of an acute infection. There was a large abscess cavity in the anterior part of Trautmann's triangle which extended forward through the retrolabyrinthine cells into the space between the cortical layer of the posterior fossa and the lean end of the posterior vertical canal. The abscess had considerably eroded but had not perforated the capsule of the posterior canal, and had broken through the cortex of the posterior fossa in a few places. The lumen of the abscess was small and contained polymorphonuclear leukocytes; its walls consisted of a thick layer of granulation tissue, which was heavily infiltrated in its central parts with polymorphonuclear leukocytes. In the peripheral parts the granulation tissue showed a more fibrillar character and contained less numerous vessels and only few leukocytes. There were no signs of progressive osteoclastic destruction of the bone which surrounded the cavity; in many places the inner surface of the bone was covered with a network of newly formed weblike fibril bone. The adjacent marrow spaces showed a gradual transformation of the bone marrow into granulation tissue. Such marrow spaces extended along the posterior fossa almost to the internal auditory meatus. In addition a large pneumatic cell was seen, just in front of the abscess, which was lined with hyperplastic mucosa without evidence of marked inflammation. There was a large accumulation of pus between the dura of the posterior fossa and the cortical layer. The dura was markedly thickened, covered on its outer surface with granulation tissue and heavily infiltrated with polymorphonuclear leukocytes. The inner surface was covered with polymorphonuclear leukocytes and fibrin.

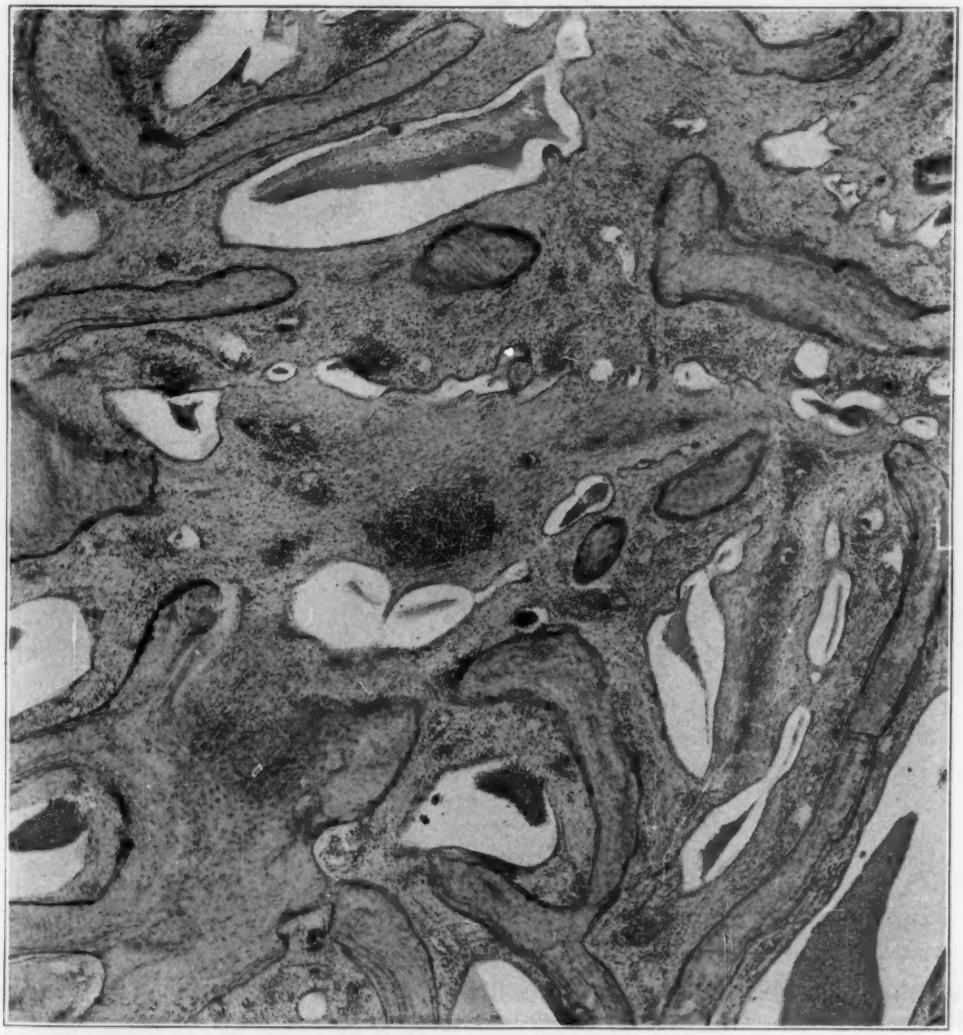

Fig. 7 (case 4).—Horizontal section showing mastoid cells. The mucosa is thickened, fibrillar and infiltrated with round cells. Some cells contain cystic organization tissue.

(*c*) Left inner ear: There was beginning meningogenic serofibrinous labyrinthitis.

(*d*) Left internal auditory meatus: There was purulent exudate in the fundus and in the arachnoidal sheaths of the nerves, and in some places there was marked polymorphonuclear infiltration between the nerve fibers and the cells of the vestibular ganglion. The purulent infiltration could be traced along the nerve and vascular channels of the modiolus and the vestibular nerves into the perilymphatic spaces of the inner ear.

(*e*) Right temporal bone: The middle ear was normal. There was beginning meningogenic serofibrinous labyrinthitis.

Summary.—In a 45 year old patient left-sided otitis media developed, which seemed to clear up within a few days after myringotomy. Two months later he suddenly presented signs and symptoms of purulent meningitis (drum membranes were normal!) and died a few hours later.

The histologic examination showed in the middle ear only few remaining signs of acute infection. The mastoidal pneumatization was well developed. The cells in the anterior part of Trautmann's triangle and the retrolabyrinthine cells had been transformed into a big abscess cavity. The capsule of the lean end of the posterior vertical canal had been eroded, but this process had come to a standstilll. Progressive erosion of the internal cortical layer had led to formation of au epidural abscess of the posterior fossa from which the infection spread to the leptomeninges and from there to both labyrinths.

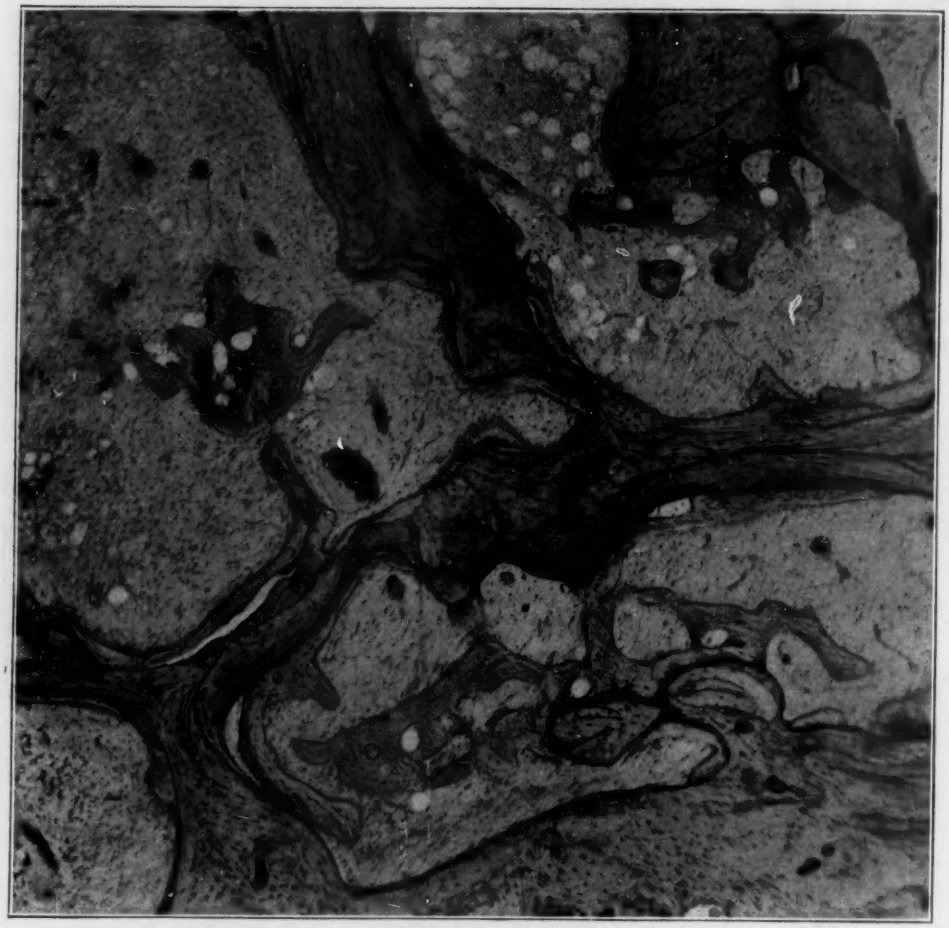

Fig. 8 (case 5).—Vertical section through the petrosal tip. Note fibrosis of the bone marrow, apposition of osteoid to the walls and formation of weblike fibril bone within the marrow spaces.

CASE 5

History.—W. T., a man aged 65, was admitted to the Presbyterian Hospital on Oct. 29, 1935. He had had a discharging right ear for three and a half weeks; the onset occurred with slight pain and marked deafness.

Physical Examination.—The left ear was normal. The right ear showed some drooping of the posterosuperior wall of the external canal and intense redness of the posterosuperior portion of the drum membrane. There was a perforation in the inferior part of the drum membrane with a thick purulent discharge. There was no tenderness over the mastoid process.

Course.—Simple mastoidectomy was performed the following day. On removal of the cortex thick creamy pus escaped under pressure. The mastoid process was well pneumatized; the cells were filled with pus and granulations. There was extensive destruction of the intercellular septums, particularly in the tip. The dura in Trautmann's triangle was pathologically exposed and covered with granulations. Culture of material from the mastoid cells showed Pneumococcus type III. The patient had a smooth postoperative course for nine days. On the tenth day he had a chill, followed by an elevation of temperature to 104 F. Culture of blood taken at that time showed Streptococcus haemolyticus. The patient was operated on the next day with the idea of tying the jugular vein. The lateral sinus could not be located. The dura of the middle fossa was exposed and found normal. The jugular vein was not exposed on account of the poor condition of the patient. Two days after this, the patient showed

signs of meningitis, the spinal fluid was cloudy and culture of the fluid showed Pneumococcus type III. A third operation was undertaken in order to achieve better drainage. The dura of the posterior and middle fossae was incised, and a small amount of pus was seen escaping from the surface of the cerebellum; the patient died the following day. Autopsy showed suppurative meningitis. The right sigmoid sinus was completely absent (Waltner [2]).

plastic, hyperemic and infiltrated, mostly with round cells. There was a moderate amount of serous exudate in the middle ear cavity with some round cells. The niches of the windows and other recesses were lined with hyperplastic fibrillar mucosa, which formed deep folds and bands. The lumens of the recesses contained in many places masses of organized tissue, which were connected with the mucosa of the walls by numerous small tissue bridges. The ossicles were embedded in "hyperplastic" mucosa. The petrosal tip consisted of

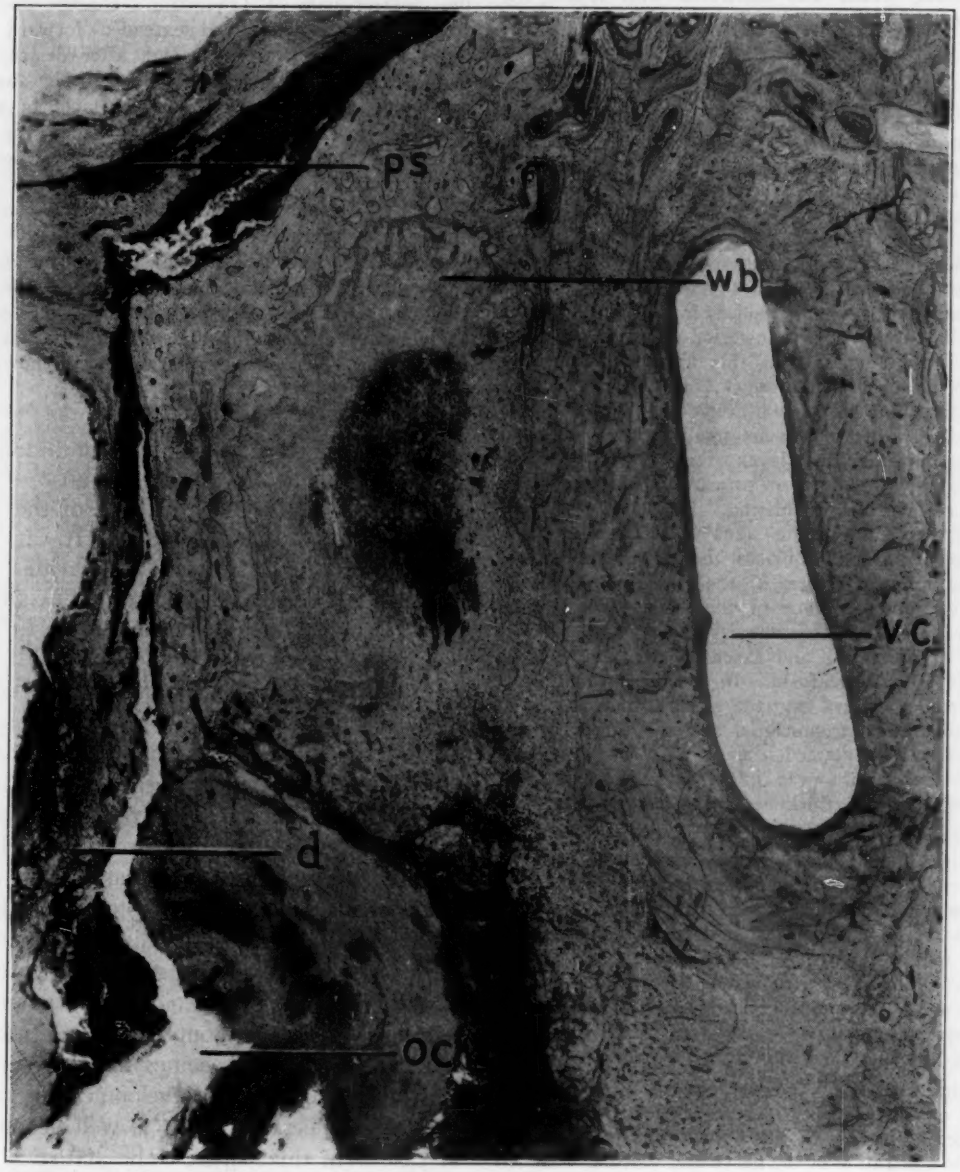

Fig. 9 (case 5).—Vertical section showing the deep abscess of the posterior fossa. *w b* indicates a network of newly formed weblike fibril bone; *o c*, the operative cavity; *v c*, the posterior vertical canal; *d*, the infiltrated dura of the posterior fossa; *p s*, the superior petrosal sinus with thrombophlebitic changes.

Histologic Examination of the Temporal Bones (right in vertical and left in horizontal serial sections).—(*a*) Right middle ear: The mucosa was strikingly hyperdiploic bone, and there were only a few pericarotid cells lined with "hyperplastic" mucosa. The marrow spaces contained chiefly fat marrow and in some places hemopoietic marrow. In a great many of the marrow spaces the original marrow was being replaced by fibrillar marrow. In early stages of this transformation the fibrillar tissue was loose and edematous; later

2. Waltner, J. G.: Anatomic Variations of the Lateral and Sigmoid Sinuses, Arch. Otolaryng. **39**:307 (April) 1944.

the edema decreased and the fibrillae became more numerous. In these areas many trabeculae were lined with a layer of osteoid, and in addition there was in some places formation of a network of weblike fibril bone (fig. 8).

(*b*) Right mastoid process: The operative cavity was covered with superficially necrotic granulation tissue. Some pneumatic cells were left, most of which were located in the depth of the sinodural angle and between the semicircular canals. The cells were filled with thick mucosa, which was infiltrated with leukocytes. In some of the cells organization tissue with cyst formation was seen; others contained a sanguinopurulent exudate. A recess of the abscess cavity which was found in Trautmann's triangle at the time of operation extended forward behind the posterior vertical canal into a large cavity. This cavity (fig. 9) extended upward into the neighborhood of the superior petrosal sinus, downward along the entire posterior aspect of the petrous bone and forward to the level of the endolymphatic sac. The cavity was filled with granulation tissue, and there was an extensive network of newly formed weblike fibril bone in the walls of the cavity. The granulation tissue extended from below toward the ampullated end of the posterior semicircular canal. The labyrinthine capsule in this area was markedly eroded, being only 1 mm. thick, but there was little evidence of active osteoclastic destruction. The surface of the bone showed numerous small lacunas, many of which were lined with a layer of newly formed pink-staining bone with a layer of osteoblasts, but osteoclasts were almost completely missing. The bone surrounding the cavity showed the signs of progressive rarefying osteitis. In two places the granulation tissue broke through the cortex of the posterior fossa and covered the outer surface of the dura, thus forming an epidural abscess. This abscess lay in the upper part of the posterior fossa and extended over the petrous ridge into the middle fossa. In this area small veins leading from the dura into the superior petrosal sinus showed fresh thrombophlebitis, and the lumen of the sinus itself also contained a fresh thrombus. In several places the dura was infiltrated with leukocytes throughout its entire thickness, thus leading to purulent infection of the leptomeninges.

(*c*) Right inner ear: There was some purulent exudate in the scala tympani, especially in the basal coil. The membranous structures of the cochlea were well preserved. The cochlear aqueduct contained some purulent exudate in its peripheral portion; its central portion contained a fine network of connective tissue but only a few pus cells. The utricle, the saccule and the semicircular canals were well preserved. The endolymphatic sac and duct showed no pathologic change.

(*d*) Right internal auditory meatus: There was purulent exudate in the internal auditory meatus and leukocytic infiltration of the nerves. There was some leukocytic infiltration of the nerve and vascular channels of the modiolus and of the vestibule.

(*e*) Left middle ear: No pathologic changes were noted.

(*f*) Left inner ear: Beginning serofibrinous meningogenic labyrinthitis was present.

(*g*) Left internal auditory meatus: This meatus contained purulent exudate, which was more abundant in the fundus; there was purulent infiltration of the cochlear and vestibular nerves, but only a few leukocytes invaded the nerve and vascular channels of the modiolus and the vestibule.

Summary.—Simple mastoidectomy was performed in a 65 year old patient because of right-sided acute otitis media with mastoiditis. The mastoid process was well pneumatized, and a large epidural abscess in Trautmann's triangle was found. Ten days later, after an uneventful postoperative course, septicemia and purulent meningitis developed.

The histologic examination showed the perilabyrinthine cells well developed and infected. A slowly progressive granulating inflammation in the cells of the anterior part of Trautmann's triangle and in the retrolabyrinthine cells had extended forward around the posterior vertical canal and, after destroying the intercellular septums, had produced a big abscess on the outside of the internal cortical layer of the posterior fossa. By way of rarefying osteitis the capsule of the ampullated end of the posterior vertical canal had been eroded but not perforated. The internal cortical layer had been perforated in two places, and an epidural abscess of the posterior fossa had been formed which extended upward into the neighborhood of the superior petrosal sinus, with subsequent thrombophlebitis of this sinus. A purulent infiltration of the dura had led to diffuse leptomeningitis with beginning bilateral serofibrinous meningogenic labyrinthitis.

COMMENT

The peculiar tendency of Pneumococcus type III infections to form a deep abscess of the posterior fossa (present in each of the 5 cases reported here) is well known. It can be explained by the histologic peculiarities of the infection. The clinical picture of Pneumococcus type III infections is not uniform. In a large percentage of cases it is identical with that of an ordinary Str. haemolyticus infection. In other instances it shows the characteristic protracted course with few symptoms. The initial symptoms are not prominent; sometimes they are so insignificant—even confined to a slight pain in the ear—that they are completely overlooked by the patient. In cases with mastoid involvement the initial symptoms are followed by a period in which the disease remains in a latent stage. It seems to subside but progresses actually into the mastoid process and even beyond that part without causing alarming clinical symptoms. It becomes manifest only after cortical perforation or development of an intracranial complication. This is well demonstrated in case 4 in this paper. The statistical figures about the frequency of this course show great variations. Among 290 operative cases in Vienna, Austria, 58 per cent showed the protracted course (Altmann [3]). A similar percentage was found by other Middle and North European authors. In the United States this course seems to be less frequent. Maybaum

3. Altmann, F.: Zur Pathologie and Klinik der akuten Mastoiditis, Monatschr. f. Ohrenh. **70**:146, 1936.

and Druss [4] observed it in only 22 per cent of their cases. Unless this low figure is only incidental, referable to the small number of the cases examined by the two authors, it would be well conceivable that geographic and climatic factors are responsible for these differences.

The cases with the typical clinical picture show a characteristic histologic picture which is different from that of an ordinary Str. haemolyticus infection.

There is only a short initial exudative inflammatory stage. It is followed by a predominantly proliferative inflammation of the mucosa of the middle ear, with early and marked proliferation of the connective tissue but with only moderate swelling and hyperemia. There is only a moderate amount of viscid exudate in the lumen of the middle ear. The mucosa of the eustachian tube after the initial stages is more or less completely free from inflammation. There is a well marked tendency toward organization of the exudate by way of ingrowth of young connective tissue, which leads to extensive formation of areas of organized tissue. These masses of newly formed tissue fill out the recesses of the middle ear cavity and surround the chain of ossicles. These changes cause the marked conduction deafness, which recedes only slowly; they account also for a common observation in otitis caused by Pneumococcus type III, the lack of improvement in hearing after air inflation in a patient with a clinically subsiding infection of the middle ear. These histologic changes, which are somewhat similar to those described by Wittmaack [5] as "hyperplastic constitution" of the mucosa of the middle ear, were present in each of our 5 cases. In a considerable percentage of cases (72 per cent, Wirth; [6] 83 per cent, Page [7]) the infection of the middle ear subsides spontaneously. In others the mastoid cells become infected while the infection of the middle ear continues or gradually recedes.

The changes in the mucosa of the mastoid cells are similar to those in the mucosa of the middle ear. As a rule, only certain groups of cells and not the entire pneumatic system are affected. The diseased cells are mostly peripherally located and separated from each other by cells with more or less normal mucosa. In the affected areas the bone is extensively destroyed. This is accomplished by lacunar erosion of the outer surface of the intercellular septums and simultaneously by rarefying osteitis of the interior of the septums, originating in the perivascular spaces. This rarefying osteitis is regarded as a reaction to the transmission of certain trophic stimuli from the diseased mucosa (Wittmaack [5]). The destruction of bone is accompanied by new formation of bone which is much more extensive than in streptococcic infections. The newly formed bone in the osteoid stage is soft and easily removable with curets. Only this newly formed bone is soft. "Softening" of regularly calcified bone, which could be brought about only by way of halisteresis, does not occur. When trabeculae are being destroyed, they become brittle but not soft. The common statement that "progressive softening" of bone is one of the characteristics of mastoiditis caused by Pneumococcus type III is a misinterpretation of the histologic changes. In the manner described, the bone is slowly but more or less completely destroyed, sometimes with formation of minute sequestrums. Formation of larger sequestrums does not belong to the typical picture and was completely missing in our 5 cases. The opinion that Pneumococcus type III has a predilection for the well pneumatized mastoid process was voiced by Stütz [8] and frequently repeated thereafter but has not remained undisputed (Wirth,[6] Vogel,[9] Richter,[10] Altmann [3] and others). Altmann, for example, found among 723 patients operated on for streptococcic mastoiditis 56 per cent with practically normal pneumatization of the mastoid process and 32 per cent with slightly impeded pneumatization, i. e., with normal extension but with marked irregularity in the arrangement of the pneumatic system. Among 270 patients suffering from infection with Pneumococcus type III only 45 per cent showed absolutely normal and 44 per cent slightly impeded pneumatization. Among the 5 patients described in this paper 4 showed good and 1 moderately impeded pneumatization.

The marked tendency of the mastoidal infection toward peripheral spread is most probably due to the considerable swelling and hypertro-

4. Maybaum, J. L., and Druss, J. G.: Otitic Infections Due to the Pneumococcus Type III, Arch. Otolaryng. **30**:21 (July) 1939.

5. Wittmaack, K., in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, vol. 12, p. 200.

6. Wirth, E.: Studien zur klinischen Bakteriologie der akuten Mittelohrentzündung, Beitr. z. Anat., Physiol., Path. u. Therap. d. Ohres **26**:190, 1928.

7. Page J. R.: Bacteriology of Acute Infections of the Middle Ear and Mastoid, Arch. Otolaryng. **20**:447 (Oct.) 1934.

8. Stütz: Siebenjährige Erfahrungen über die durch den Streptococcus mucosus hervorgerufene Otitis media acuta, Beitr. z. Anat., Physiol., Path. u. Therap. d. Ohres **7**:100, 1913.

9. Vogel, K.: Erfahrungen über Mukosusotitis, Ztschr. f. Hals-usw. Heilk. **22**:357, 1929.

10. Richter, H.: Warzenfortsatzpneumatisation und Mucosuseiterung, Ztschr. f. Hals-, Nasen- u. Ohrenh. **25**:74, 1929.

phy of the mucosa in the antrum and the diseased cells and the extensive formation of organization tissue in the lumens. Both factors impede the drainage toward the middle ear cavity (see cases 2, 3 and 4). In cases in which well developed cells are present around and behind the labyrinth, such as in the 5 cases of this paper, the infection frequently progresses through them toward the posterior surface of the petrosa. Owing to lack of drainage, the destruction of the cells is frequently accompanied by abscess formation. Almost invariably, as in all of our 5 cases, the dura of the posterior fossa becomes exposed in this area.

Clinical and anatomic experience, as well as study of the cases reported in this paper, shows that the extension toward the posterior fossa may take place along several routes. The most frequent one is that along the retrolabyrinthine cells (cases 2, 4 and 5). In other instances (case 3) the route lies from the epibulbar-infralabyrinthine cells around the labyrinth and sometimes along the cells of the sinodural angle (case 1).

The abscesses show a definite tendency toward expansion. They grow not only by destruction of the pneumatic cells but also by gradual erosion of the surface of the labyrinthine capsule. The erosion is frequently accompanied by deposition of newly formed bone. The adjacent areas of the bone show reactive rarefying osteitis, which sometimes leads to extensive destruction of the capsule. The resorption spaces are free from infection in the beginning, but when the destruction reaches the outer surface, the resorption spaces come in direct contact with infected mucosa and become themselves secondarily infected. The destruction of the capsule is in certain cases so extensive that a labyrinthine fistula or even several fistulas are formed.

Since the posterior vertical canal lies in the immediate neighborhood of the abscess, it is easily understandable that this canal is most frequently affected (cases 2, 3, 4 and 5). Sometimes the superior vertical canal is eroded (case 1), and occasionally the rarefying osteitis in the neighborhood of other perilabyrinthine cells leads to erosion or even destruction of other parts—in case 2, for instance, to a fistula in the lateral semicircular canal.

The diploic bone of the tip shows also not infrequently reactive changes (cases 4 and 5). These consist chiefly of fibrosis of the bone marrow with new formation of weblike fibril bone within the marrow spaces and apposition of osteoid to the walls. The new formation of weblike fibril bone within the marrow spaces is frequently called "metaplastic," but this is not correct. Wherever and whenever true bone is formed, it is formed by specific cell elements, the osteoblasts, and not by direct transformation of an already differently differentiated tissue into bone tissue.

The deep abscess of the posterior fossa expands most frequently toward the dura of the posterior fossa, with or without subsequent infection of the leptomeninges, or toward the vertical semicircular canals or toward both. It may extend forward into the roof (cases 1 and 3) or the posterior wall (cases 1 and 2) of the internal auditory meatus, or it may break through into the lumen of the meatus. Growing upward, the abscess may extend to the dura of the middle fossa (case 3); growing downward, it may reach the bulb of the jugular vein (case 3). The formation of a labyrinthine fistula leads to various consequences as follows:

1. In the majority of cases the exposed endosteum undergoes proliferation, and toxic substances diffusing from the infected areas into the labyrinthine fluid cause a serofibrinous exudate to appear in the adjacent parts of the perilymphatic space. Soon the exudate is organized, and the process comes to a standstill.

Clinically the formation of the fistula may remain unnoticed, or it may manifest itself by attacks of dizziness and nystagmus and possibly by a positive fistula symptom. In many instances the latter is absent (cases 2 and 3), particularly when the fistula is far away from the middle ear and separated from it by masses of granulation tissue. The serofibrinous exudate in the perilymphatic space is accompanied by more or less outspoken signs of serous labyrinthitis, which subsides as soon as the break through is walled off by the growth of granulation tissue into the exudate in the perilymphatic space.

The further course depends on whether or not sufficient drainage has been established in this stage. In the first instance the process has a fair chance to heal up. This was seen by one of us (F. A.) in 3 cases of Pneumococcus type III infection in which the breaking through into the posterior vertical canal was accompanied by a vertical fistular symptom and in which a complete cure was observed after simple mastoidectomy with sufficient drainage of the retrolabyrinthine and infralabyrinthine cells. When the drainage is not sufficient, the bacteria will gradually penetrate into the originally sterile granulation tissue which fills out the fistula and eventually from there into the intralabyrinthine fluids, thus causing purulent or necrotizing labyrinthitis (cases 2 and 3).

2. In another group of cases, much less numerous, the formation of granulation tissue in the lumen of the semicircular canal progresses beyond the site of the fistula. Chronic progressive granulating otitis interna develops, and the labyrinthine cavities are gradually filled with granulation tissue. In the course of the disease the cochlear and vestibular functions are eventually completely lost. In some instances attacks of dizziness and nystagmus are observed; in others these symptoms are missing. These are the cases of more or less "symptomless loss of labyrinthine function." If the drainage is unsatisfactory, this form may also terminate in purulent or necrotizing labyrinthitis.

3. In a further group of cases the break-through is immediately followed by diffuse purulent (case 1) or necrotizing labyrinthitis.

In the purulent form the contents of the labyrinth remain at least partly viable. When no meningitis develops, the exudate becomes partly or even completely organized by ingrowth of organization tissue from the intact parts of the labyrinthine contents. In certain cases the labyrinthine cavities are in a short time filled with connective tissue or even with bone. In others, in which as a rule the process follows chronic infection of the middle ear, the labyrinthitis becomes chronic. It lasts for a long time, and the organization of the exudate is interrupted by repeated flare-ups of the purulent infection.

Cases of necrotizing form are divided into two groups: those in which the necrosis of the contents of the labyrinth is preceded or accompanied by purulent inflammation (so-called purulent necrotizing form, Zange [11]) and those in which the purulent inflammatory reaction is more or less completely missing (inflammatory necrosis of the membranous labyrinth, Zange [11]). If in these cases spontaneous healing occurs, it is brought about by ingrowth of granulation tissue from the outer surface of the labyrinth, which requires a long time; in the majority of the cases, however, meningitis develops before organization takes place. The necrotizing form is frequent in cases of Pneumococcus type III infection and occurs in about 50 per cent of the cases in which diffuse labyrinthitis develops.

The meningitis which in about one half of the cases follows the diffuse labyrinthitis may develop from spread of the infection directly to the meninges along the vascular and nerve channels of the cochlea and of the vestibule or in rare instances from extension by way of the endolymphatic duct and sac or the cochlear aqueduct. In other cases the spread of the infection is halted in the arachnoidal cisterna in the fundus of the internal auditory meatus. An abscess is formed (*Gehörgangsgrundabszess*, Politzer [12]) and walled off by a more or less resistant layer of granulation tissue. The formation of this abscess represents a kind of defensive mechanism; it is an attempt at prohibiting the infection from reaching the leptomeninges. In many cases this attempt is unsuccessful, the infection penetrates the abscess wall and the meninges are invaded. In some cases the abscess damages the vessel in the fundus and interrupts the blood supply to the labyrinth; this is followed by the so-called secondary necrosis of the labyrinth, a rare event in labyrinthitis caused by Pneumococcus type III. The clinical picture of the meningitis caused by Pneumococcus type III is frequently different from that caused by Streptococcus. The meningeal signs appear later and are less numerous and pronounced (see case 2; also Smith [13]). They may even be completely missing at a time when, as proved by autopsy, diffuse purulent leptomeningitis is present (case 3).

The cases described in this paper show marked differences in genesis of the meningitis.

In case 1 the breaking through the labyrinthine capsule was apparently immediately followed by purulent labyrinthitis and by invasion of the leptomeninges, the bacteria advancing through the internal auditory meatus. At the time when the operation was performed even complete drainage of the diseased cells would have been insufficient. Only drainage of the labyrinthine cavities themselves could have been successful.

In case 2 most probably the break-through occurred five weeks after the onset of the infection, shortly before or at the time when the signs of serous labyrinthitis became manifest. At this stage simple mastoidectomy was performed, but the diseased retrolabyrinthine cells were not sufficiently drained. The serous labyrinthitis progressed into diffuse purulent infection. The latter was followed by formation of an abscess in the fundus of the internal auditory meatus, a rare event in Pneumococcus type III infections. The demarcation toward the medial

11. Zange, U.: Die pathologische Anatomie und Physiologie der mittelohrentspringenden Labyrinthentzündungen, Wiesbaden, J. F. Bergmann, 1919; Die konservative und chirurgische Behandlung der entzündlichen Erkrankungen des Innenohres mit besonderer Berücksichtigung der Indikationsstellung, Ztschr. f. Hals-, Nasen- u. Ohrenh. **18**:1, 1927.

12. Politzer, A.: Labyrinthbefunde bei chronischen Mittelohreiterungen, Arch. f. Ohrenh. **65**:161, 1905.

13. Smith, S. M.: A Discussion of Meningitis, Laryngoscope **32**:465, 1922.

part of the internal auditory meatus was not as yet very strong, and the spread of the infection toward the leptomeninges was only temporarily stopped. The longer duration of the labyrinthitis in this case is proved by the fact that the annular ligament of the stapes and the membrane of the round window were destroyed and that in some places osteoclastic destruction of bone was taking place on the inner surface of the semicircular canals. In addition to these changes there was a spread of the infection to the leptomeninges from an epidural abscess of the posterior fossa by penetration of the dura in that region. The meningeal signs appeared strikingly late, only a few hours before the death of the patient.

In case 3 the symptoms of serous labyrinthitis developed seven weeks after the onset of the middle ear infection. At that time probably a labyrinthine fistula had already been present and a serofibrinous exudation into the perilymphatic space was taking place. Shortly thereafter the break-through was walled off and the symptoms subsided. Simple mastoidectomy was performed, but the diseased infralabyrinthine cells were not sufficiently drained. Six weeks later diffuse purulent necrotizing labyrinthitis developed which through the vascular and nerve channels of the vestibule and the cochlea rapidly led to diffuse leptomeningitis. The complete absence of clinical signs of meningitis deserves particular mention.

In cases 4 and 5 the meningitis developed from an epidural abscess of the posterior fossa by direct penetration of the dura without infection of the labyrinth.

In none of the cases did the infection spread to the leptomeninges mainly through the cochlear aqueduct or the endolymphatic duct.

The annular ligament of the stapes was twice partly (cases 1 and 3) and once completely destroyed (case 2). The mucosa which lined the oval window showed acute inflammatory infiltration but was otherwise intact. The membrane of the round window and the covering mucosa were infiltrated with leukocytes in cases 1 and 3. In case 2 the membrane was replaced by a plug of granulation tissue which completely filled out the niche of the round window. The marked resistance of the mucosa of the window in acute and chronic purulent and necrotizing labyrinthitis has clinical significance. It prevents drainage into the middle ear and thus facilitates the spread toward the leptomeninges.

In all the cases in which both temporal bones were examined (cases 1, 4 and 5) there was evidence of a meningogenic infection of the labyrinthine cavities on the opposite side, too. It was most marked in case 1. But even there, owing to the short duration, it had not progressed beyond the beginning stage. In case 4 it was still less marked, and in case 5 there was only slight serofibrinous inflammation.

The main pathway of the meningogenic infection in all the 3 cases extended along the vascular and nerve channels, particularly through Rosenthal's canal into the scala tympani. The cochlear aqueduct played only a minor role in the examined cases.

In practically all cases of typical Pneumococcus type III otitis the infection of the labyrinth develops through one or several of the semicircular canals. It is a late complication, occurring several weeks or even months after the onset of the middle ear infection (ten weeks in case 1; five weeks in case 2; seven weeks in case 3). Among 17 cases collected by Zange [11] the posterior vertical canal was the site of the break-through from an extradural abscess of the posterior fossa eleven times, the superior vertical canal three times and the lateral canal three times. Erosion of the cochlea is rare. Infection spreading through the windows in the early days of the otitis is not seen in typical cases of Pneumococcus type III infection. It is common in cases of otitis due to Streptococcus and in cases of otitis due to Pneumococcus type III without protracted course and with marked exudative inflammatory changes in the middle ear.

Summarizing, we may say that the greatest danger for the labyrinth in the classic Pneumococcus type III infection lies in the formation of a deep abscess of the posterior fossa with subsequent erosion of one of the vertical canals, most frequently the posterior vertical.

Labyrinthine involvement is more frequent in Pneumococcus type III than in streptococcic infections. It was observed by Hesse [14] in 10 per cent of all surgical operations for mastoiditis caused by Pneumococcus type III. Maybaum and Druss [4] noted definite involvement of the labyrinth in 4 per cent of the cases. If the cases with "clinical evidence of mild labyrinthine irritation" actually are cases of labyrinthine involvement and not only cases of perilabyrinthitis or paralabyrinthitis, the incidence would be 9 per cent. According to our experience, these figures, derived from a small number of cases, seem too high. Altmann [3] found labyrinthine involvement in 3 per cent among 168 operative cases as compared with 1 per cent in 1,029 operative cases of otitis due to Strepto-

14. Hesse, W.: Beiträge zur Bakteriologie und Klinik akuter Mittelohreiterung, akuter Mastoiditiden und deren Komplikation, Ztschr. f. Hals-, Nasen- u. Ohrenh. **22**:372, 1929.

coccus. The figure of 1 per cent given in his paper [15] for otitis media caused by Pneumococcus mucosus was arrived at by considering only the cases of diffuse and not those of circumscribed labyrinthitis.

Thus, even according to conservative estimates, the involvement of the labyrinth is three times as frequent as in streptococcic infections.

In considering the anatomic and clinical peculiarities of the Pneumococcus type III infection the conclusion seems evident that the only way to prevent infection of the labyrinth with its frequently deleterious consequences is by thorough exposure and systematic removal of the perilabyrinthine cells, no matter whether they appear macroscopically diseased or healthy, whenever mastoidectomy is performed. Careful preoperative roentgen studies may be a valuable help in achieving this goal.

We fully agree with Maybaum and Druss [4] that the sinodural angle, the perilabyrinthine region and any suggestive tract leading into the petrous pyramid should be thoroughly exenterated and the semicircular canals thoroughly skeletonized. This postulate must be fulfilled whether chemotherapy was used before or will be used after the operation. Conservatism in these cases based on overconfidence in the efficiency of chemotherapy could lead to complete loss of function of the diseased ear. At this place, however, we want to reiterate that in our experience, contrary to that of Dean,[16] mastoidectomy is necessary in only a minority of cases. We agree with Page [7] that the "bad reputation" of Pneumococcus type III should not be an inducement for operation in cases in which the clinical symptoms clearly point to subsidence of the infection.

It would be beyond the scope of this paper to discuss the exact indications for surgical treatment of the labyrinth. The ultimate aim of drainage of the labyrinth is to prevent spread of the infection to the meninges. It is done only in cases in which the function of the labyrinth is definitely completely lost. The excellent results of chemotherapy in the prevention and the treatment of purulent meningitis are well known. It seems probable that through the appropriate use of chemotherapy previous indications for labyrinthectomy will have to be somewhat modified but at the present time our experience in this matter is not extensive enough to permit definite conclusions.

15. Altmann,[3] p. 1484.

16. Dean, L. W.: Cytological and Bacteriological Studies of Otitic Disease, Tr. Am. Otol. Soc. **22**:36, 1932.

SUMMARY AND CONCLUSIONS

In 3 of 5 cases of typical Pneumococcus type III otitis media in which the histologic changes in the temporal bones were studied, labyrinthitis developed, with purulent meningitis following. In 2 there was only erosion of the labyrinthine capsule, with infection of the leptomeninges from an epidural abscess of the posterior fossa.

Labyrinthitis follows Pneumococcus type III otitis media about three times as frequently as Str. haemolyticus infections. In about half of the cases the disease process ends in purulent leptomeningitis.

The labyrinthitis in typical cases of infection with Pneumococcus type III is usually caused by the pneumococci breaking through the wall of one or several semicircular canals. Most frequently the posterior vertical canal is affected, and the break-through is preceded by the formation of a deep abscess of the posterior fossa. The latter, in turn, develops from infection of perilabyrinthine cells, most frequently from infection of the retrolabyrinthine group, and leads almost invariably to the formation of an epidural abscess of the posterior fossa.

The tendency of Pneumococcus type III infection of the mastoid process toward peripheral spread is explained by the histologic peculiarities of the infection.

Systematic exenteration of the perilabyrinthine cells whether they appear macroscopically diseased or healthy is the only way to prevent labyrinthitis. Overconfidence in the effectiveness of chemotherapy may result in irreparable functional damage. In all cases of imminent or already developed meningitis, opening of the labyrinth has been the accepted treatment. It seems likely, however, that in view of the excellent results of chemotherapy in the prevention and treatment of meningitis the previous indications for this procedure will have to be somewhat revised.

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HISTOPATHOLOGY OF THE NASAL MUCOSA OF OLDER PERSONS

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The original purpose of this paper was to describe the influence of aging on the nasal mucosa. This purpose has been carried out provided two important factors are taken into consideration: (1) that nearly every elderly person may have experienced several inflammatory attacks on his nasal mucosa during his lifetime; (2) that the material for this study was obtained from cadavers of persons whose fatal diseases may have altered the structure of the nasal mucosa. Obviously, the latter possibility was kept in mind in evaluating the microscopic observations.

The inferior turbinates were removed from 23 cadavers of persons between 50 and 90 years of age. The causes of death varied, but in 1 person only was there a nasal disease. That person died from meningitis originating in the sphenoid sinus. Interrupted serial sections were made of the turbinal specimens and prepared for study with hematoxylin-eosin, Van Gieson, Mallory and orcein stains.

GENERAL OBSERVATIONS

Epithelium.—All types of epithelium were seen, but no definite relation could be established between the age of the subject and the type of epithelium. For example, in the nasal mucosa of a woman aged 85 years, who died of bronchial pneumonia, typical ciliated columnar epithelium was seen, presenting a moderate production of mucus, while in that of a man aged 52 years there was considerable transitional and squamous epithelium.

Interesting were (*a*) the production of mucus in the epithelium and (*b*) the migration of leukocytes through the epithelium.

With regard to the production of mucus, only in 5 specimens was there an almost total transformation of the epithelium into goblet cells (fig. 3). In 6 specimens there was a spotlike increase of goblet cells, particularly in the crypts, while in 12 specimens the production of mucus was poor or absent. From these observations one cannot conclude that the columnar epithelium is frequently incapable of producing considerable mucus. Such a conclusion would be incorrect since the transformation of a columnar cell into a goblet cell is not dependent on age but on factors such as infection, allergy and certain undetermined conditions. The observations described can be explained by the fact that the mucosa was extirpated from persons long bedridden prior to death, and under such circumstances they did not contract any nasal infections. General emaciation prior to death is another factor, since it was present in some of the persons from whom specimens were taken.

The migration of leukocytes through the epithelium was in general moderate. At no time was it as dense as in the epithelium of the tonsils; however, it was definitely seen. In some specimens there was almost no migration. In a specimen from a woman who died of pneumonia there was a considerable amount of it. In most instances in which there was no migration the reason for the lack of it was obvious. The passage of leukocytes through the epithelium depends on the development of lymphatic tissue in the subepithelial layer. In the specimens studied the lymphatic tissue was poorly developed, as will be described later; consequently there was only moderate migration through the epithelium.

Basement Membrane and Subepithelial Layer.—As usual, the basement membrane presented different thicknesses even in the same specimen. In younger persons the subepithelial layer is characterized by accumulation of leukocytes, which occasionally may even form follicles. In the specimens studied diffuse accumulation of leukocytes in the subepithelial layer was seldom seen. The leukocytes consisted of lymphocytes and plasma cells; eosinophils were rare, and polymorphonuclear cells were never conspicuous. But even in these specimens there were spots which consisted only of connective tissue (frequently presenting hyaline degeneration), with no leukocytes (figs. 1 and 2). When these changes became pronounced, large areas of the lymphatic layer were replaced by connective tissue with scattered lymphocytes (figs. 3 and 4); actual accumulations of these cells were found only on the bottoms of the crypts, around blood vessels and around excretory ducts. When these changes became more pronounced, the entire

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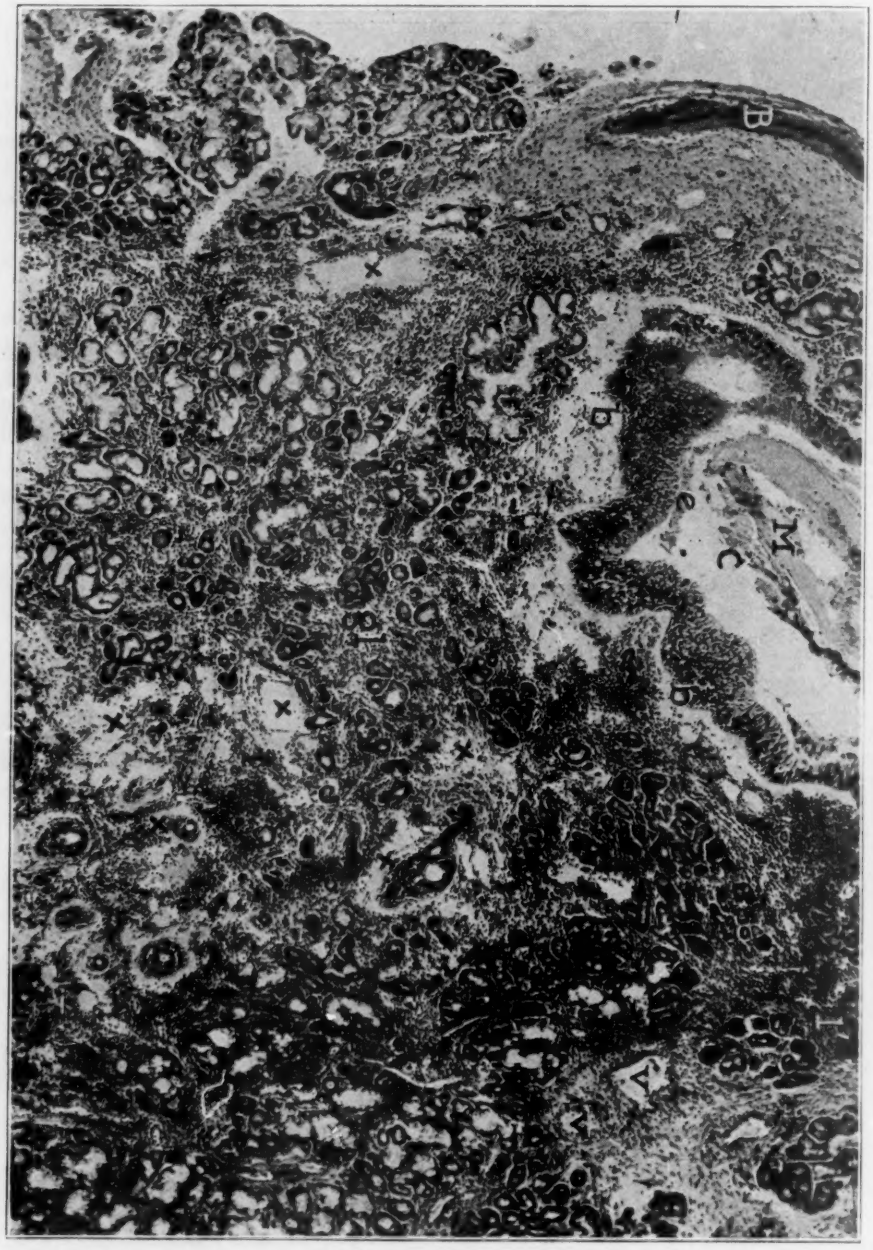
lymphatic layer was replaced by loose connective or by hyaline connective tissue. In the specimens which exemplified the latter condition there was only one thick hyaline layer beneath the epithelium, consisting of the basement membrane and the hyaline subepithelial layer. Finally, cavity consisted of firm connective tissue, containing several compressed glands. The contents of the cavity were debris, remnants of epithelium and glands. How this cavity developed is at best speculative. At first hyaline substance was deposited in the connective tissue

Fig. 1 (case 21).—Mucosa from a lower turbinate of a man 52 years of age, who died of pneumonia: *e*, very thick squamous cell epithelium forming deep crypts; *e'*, columnar epithelium; *x*, hyaline deposits in the subepithelial tissue; *b*, basement membrane; *a*, pyknocytes (described by H. Brunner and J. W. Wall [Ann. Otol., Rhin. & Laryng. **49**:688 (Sept.) 1940]); *t*, connective tissue with chronic inflammation.

in a specimen from a woman aged 78 years, who died of diabetes, myocardial degeneration and coronary sclerosis, a cavity was found in the subepithelial layer, the cavity having perforated through the epithelium (fig. 5). The walls of the of the subepithelial layer. With the increasing deposition of this substance the masses became necrotic and were expelled through a rupture of the epithelium. It is highly probable that the cavity was formed in this manner.

Connective Tissue.—The connective tissue presented differences as far as quantity was concerned. In the majority of specimens it was more abundant than it usually is in specimens from juvenile persons; the excepted specimens were those in which the corpus cavernosum was overdeveloped (see section on the corpus cavernosum). The connective tissue was loose, frequently even edematous, or it was firm. In the latter case there was frequently marked deposition of hyalin. There was, as a rule, no infiltration with leukocytes.

Elastic Tissue.—The elastic tissue presented marked individual variations as far as quantity was concerned, but there is no known relation between age and development of elastic tissue. Elastic tissue was found in the periosteum, in the venules, beneath the basement membrane, occasionally in the walls of the veins of the corpus cavernosum and freely in the connective tissue.


B
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C
b
e
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x
x

It was never seen to penetrate the basement membrane.

Bone.—Only in 9 specimens was the bone of the inferior turbinate covered with osteoblasts; in 4 it was covered with osteoblasts and osteoclasts, osteogenesis prevailing; and in 3 specimens the margins of the bone were aplastic. In 1 specimen, from a man aged 55 years, whose death was due to coronary sclerosis, encephalomalacia and bronchial pneumonia, there was thickening of the periosteum of inflammatory origin. From these observations it is evident that when bone was present in the specimens, osteogenesis was most frequently observed, osteoclasis being seen only occasionally. Even in a 90 year old man the bone of the inferior turbinate was covered with osteoblasts, resulting in definite osteogenesis.

Corpus Cavernosum.—It should be stated that the corpus cavernosum of the nasal mucosa is not an actual corpus cavernosum because (1) the afferent arterial helicines are absent, (2) there is no direct arteriovenous anastomosis, (3) the walls of the blood spaces frequently contain muscle fibers, and muscle fibers in the corpus cavernosum of the sexual organs are not in connection with the walls of the blood spaces. Thus the nasal corpus cavernosum is merely a part of the venous system of the nose, not, however, lying between the arterial and venous systems as it does in the sexual organs.

In the specimens studied the corpus cavernosum did not show any conspicuous signs although there was a definite variety of the quantitative development. Two specimens were peculiar: One from a man who died at the age of 53 years from chronic alcoholism and hepatic cirrhosis, and the other from a woman who succumbed at the age of 50 years to a perforating ulcer of the stomach and who presented at autopsy cirrhosis of the liver. In both specimens the corpus cavernosum presented an extraordinary development; it almost reached the epithelium, and between the blood spaces there was almost no interstitial tissue (connective tissue, muscles, nerves). From these facts one is able to

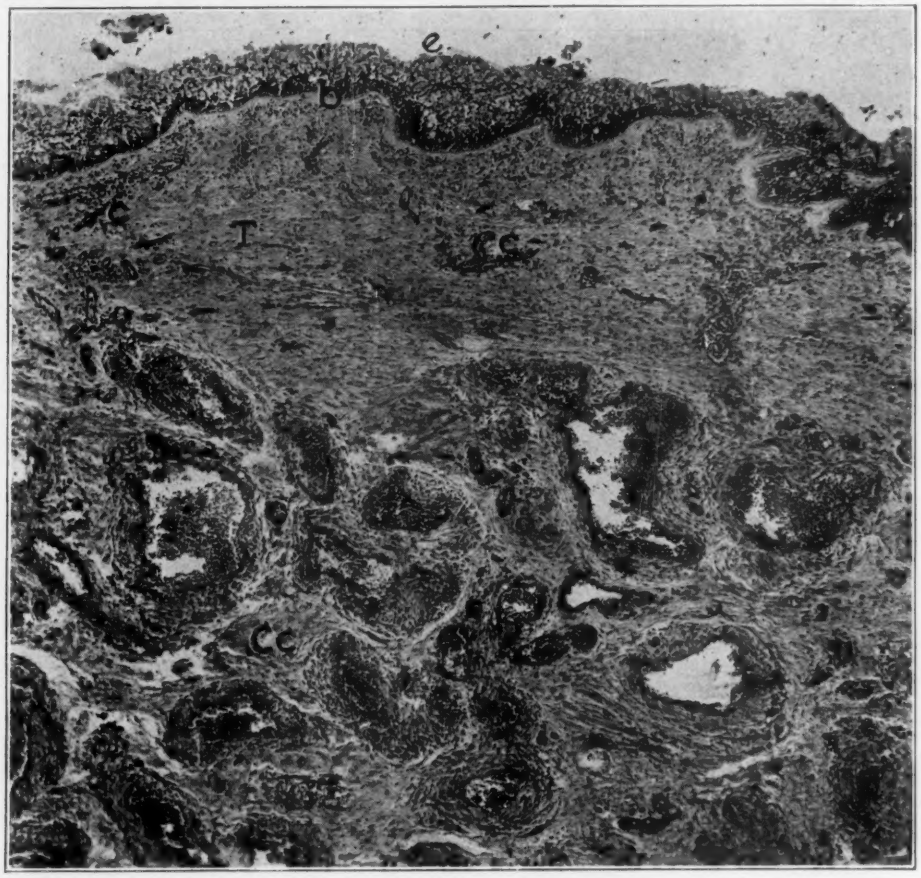

Fig. 3 (case 10).—Mucosa from a lower turbinate of a man 75 years of age, who died of myocardial degeneration and coronary sclerosis: *e*, epithelium producing a great amount of mucus; *b*, basement membrane; *T*, subepithelial connective tissue without lymphatic infiltration; *c*, capillaries with a slight perivascular infiltration; *Cc*, corpus cavernosum.

conclude that the nasal corpus cavernosum may present hypertrophy in that its blood spaces become increased in number as well as in diameter at the expense of the interstitial and subepithelial tissue of the mucosa. It is noteworthy that in both cases there was cirrhosis of the liver, so that one might think of varicosities in the nasal corpus cavernosun resembling the varicosities often found in the esophagus in hepatic cirrhosis.

Principal Artery of the Inferior Turbinate.—The principal artery of the inferior turbinate is situated in the meshes of the network formed by the bony structure and is surrounded by a thick layer of connective tissue. Textbooks do not mention that frequently the artery has two muscle layers, a circular and a longitudinal. This is normal and not a sign of hypertrophy.

In a specimen from a Negro man who died at 52 years of age from cerebral hemorrhage due to hypertension, the principal artery presented a poorly developed internal elastic layer. There was, however, a considerable amount of elastic fibers in the adventitial layer, these fibers being in relation with the elastic fibers of the periosteum. In the adventitia of the artery large amounts of hyalin were deposited (fig. 6), which led to atrophy of the muscle layer of the artery.

Glands.—The glands were in various stages of activity. Active mucous glands were seen only occasionally; ruptured mucous glands as they appear in hyperplastic mucosa were not observed at all. The lymphatic accumulations around the glands were poorly developed except in specimens from persons in whom death resulted from some acute infectious process such as bronchopneumonia.

More important is the fact that frequently the excretory ducts of the glands were each surrounded by a thick ring of hyaline tissue (figs. 4 and 7). This is not unusual at the level of the basement membrane when the latter is perforated by an excretory duct. Under such circumstances the basement membrane, consisting of a hyaline band, surrounds the excretory duct. But in the specimens studied even the excretory ducts situated in the depths of the lamina propria of the mucosa were surrounded by hyaline tissue. Even more conspicuous were the changes in the glands themselves. Usually there is a fine network of connective tissue within the nasal glands, forming thin septums between the glandular acini. In the specimens of the present study frequently there was definite thickening of the septums, and

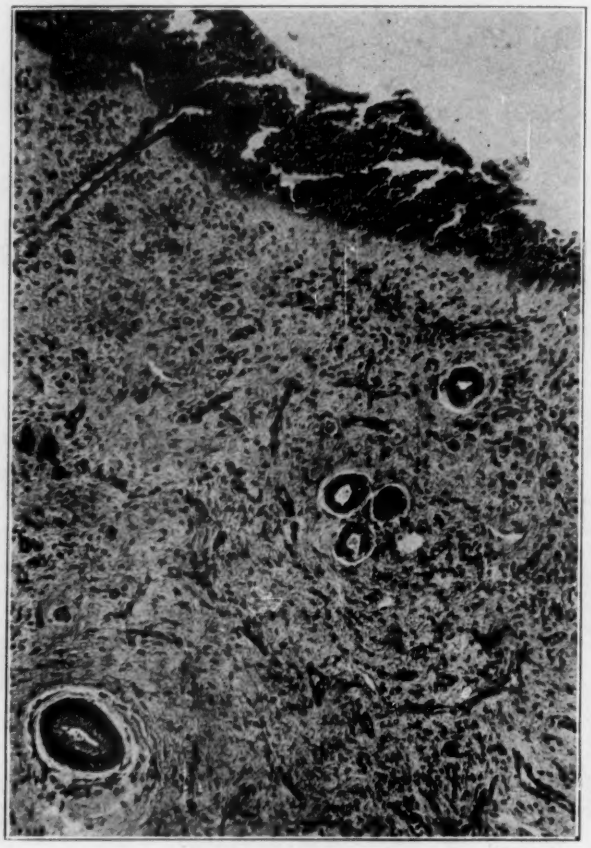

Fig. 4 (case 2).—Nasal mucosa from a man 57 years of age.

these even became hyalinized. Thickened and hyalinized septums exerted pressure on the glands, the latter becoming degenerated and atrophic (fig. 8). Onkocytes were found in 8 specimens, while in the specimens from the oldest subjects they were always found.

COMMENT

It should be emphasized that the descriptions concern only specimens from the inferior turbinates. Conclusions concerning the entire nasal mucosa can be drawn only with great precaution.

The chief alteration with age was a decrease of the lymphatic tissue in the subepithelial layer as well as about the glands (figs. 1 and 3). This observation is in accord with that in tonsils and adenoids, in which the lymphatic tissue likewise decreases with age. It should be stated, however, that some observations are contradictory and do not permit an analogy to be drawn between the lymphatic tissue of the tonsils and that of the nasal mucosa. For instance, in the specimen from a man aged 90 years, who died from carcinoma of the pancreas, a well developed lymphatic tissue, especially in the surrounding of the glands, was noted, while in the specimen from a man aged 56 years, who died of carcinoma of the esophagus, almost the entire lymphatic tissue of the subepithelial layer was replaced by hyaline tissue containing only a small number of lymphocytes. Therefore, the age factor is not the sole factor responsible for the decrease of lymphatic tissue in the nasal mucosa. Other probable important causes are the number of preceding rhinologic infections, the general physical state of the subject and the fatal disease.

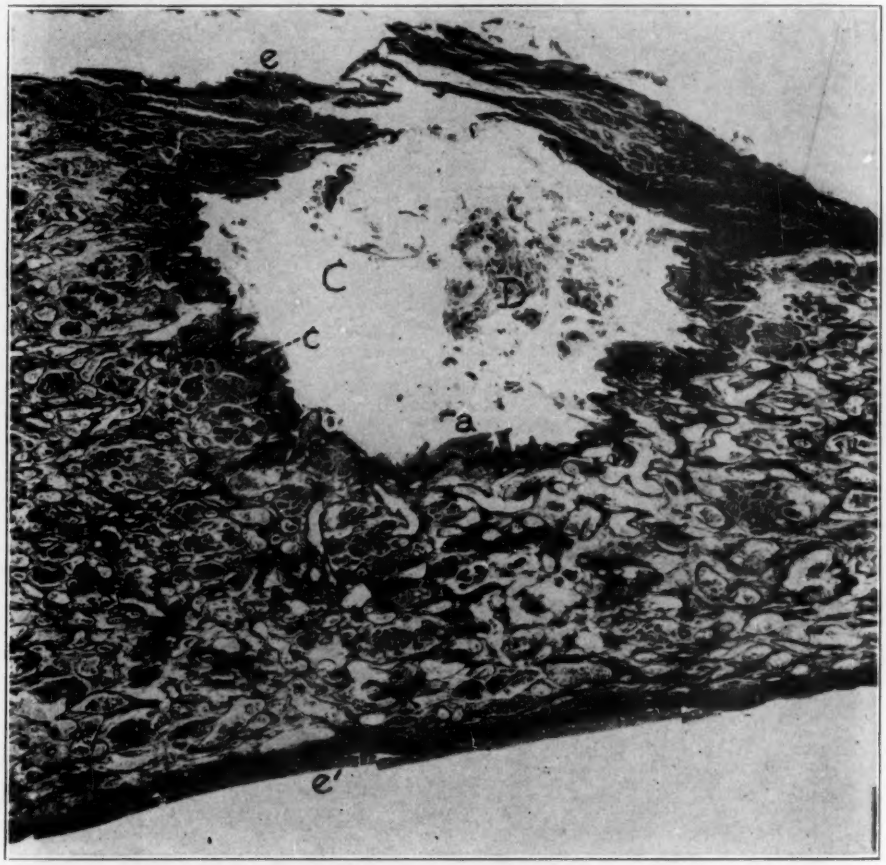

Fig. 5 (case 21).—Nasal mucosa from a woman aged 78, who died of diabetes, myocardial degeneration and coronary sclerosis: *C*, cavity in the subepithelial layer; *D*, debris; *c*, firm connective tissue; *a*, necrotic tissue; *e*, squamous epithelium; *e'*, columnar epithelium. Note the highly developed corpus cavernosum in the turbinate.

The decrease of lymphatic tissue was followed by an increase of connective tissue which replaced the lymphatic tissue, resulting in fibrosis of the mucosa. Only in instances in which the corpus cavernosum becomes hyperplastic—for example, in hepatic cirrhosis—is the fibrosis of the mucosa less marked. The fibrosis exerts a deleterious influence on the glands and on the blood vessels.

As for the glands, the connective tissue septums within them became thickened (fig. 8). The same situation occurred with the connective tis-

sue surrounding the excretory ducts. The thickened septums exerted pressure on the glands and thus interfered with their normal activity. The end result was atrophy of the glands and excretory ducts.

changes produced disturbances of the circulation, and it is quite probable that because of the disturbed circulation hyalin was deposited in the connective tissue. The hyalin was found (*a*) in the subepithelial layer, which finally blended with

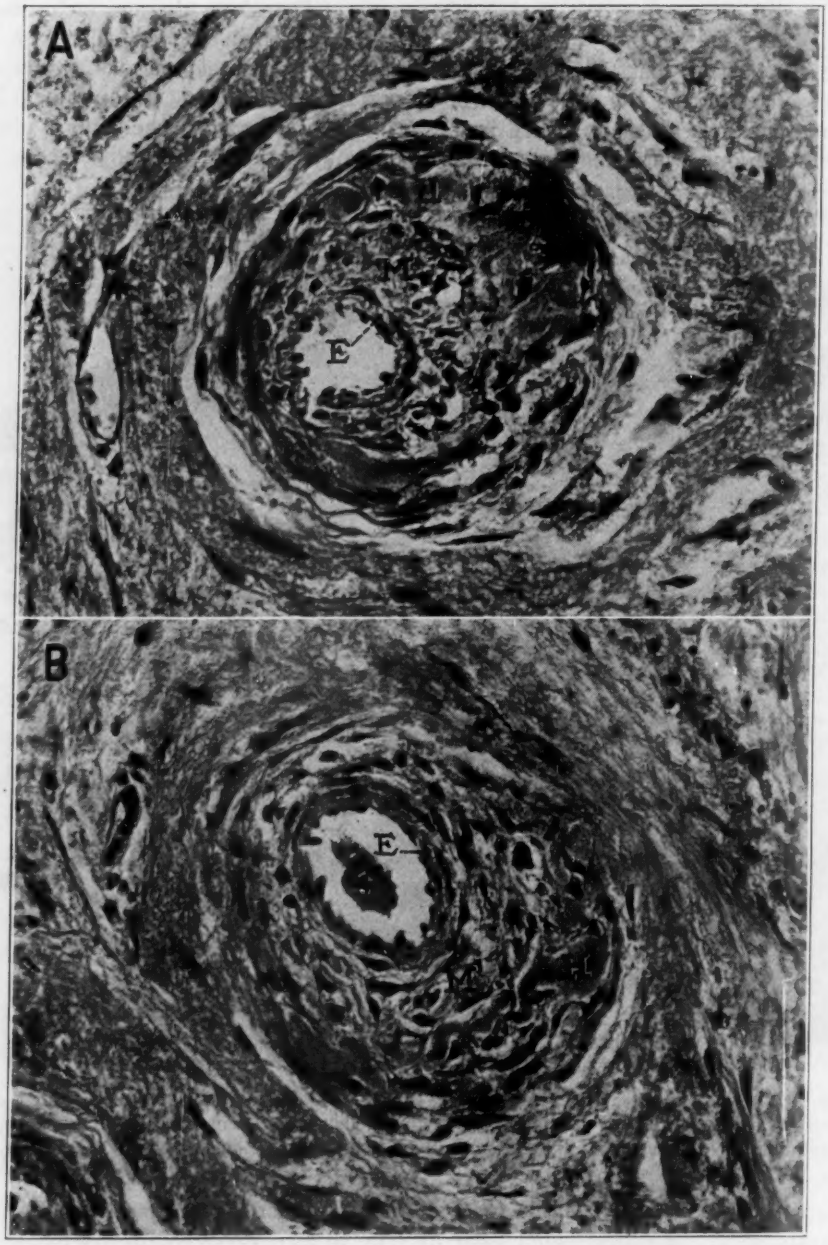

Fig. 6 (case 1).—*A* and *B*, two sections from the principal artery of a turbinate bone from a Negro 52 years of age, who died of cerebral hemorrhage and hypertensive heart disease: *E*, endothelium; *M*, muscular layer; *H*, hyalin.

In the blood vessels the connective tissue increased in the adventitia of the larger arteries. The fibrosis extended, furthermore, into the muscular layer of the arteries. The capillaries became ensheathed with a thick layer of connective tissue which almost compressed them. These

the basement membrane forming one big layer of hyaline connective tissue, (*b*) around the excretory ducts, (*c*) within the connective tissue septums of the glands, (*d*) in the connective tissue of the lamina propria and (*e*) in the adventitia of the larger arteries.

Of interest, also, was the observation of onkocytes in 8 specimens. As already mentioned, the characteristic feature in the specimens studied was a decrease in the lymphatic tissue, which was replaced by connective tissue, the latter ultimately becoming hyalinized. This very much resembles the change in atrophic rhinitis, which likewise is characterized by fibrosis of the nucosa. There are, however, clinical as well as pathologic differences between the nasal mucosa of older persons and that of patients with atrophic rhinitis. Clinically, in older persons there is observed more or less marked atrophy of the mucosa but there is neither formation of crusts nor fetor. Pathologically, the fibrosis in atrophic rhinitis actually is the formation of a firm scar following an in-

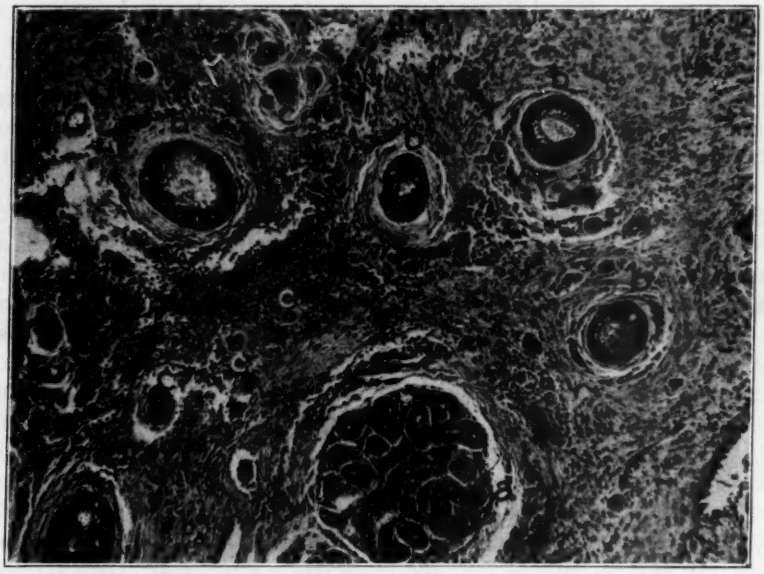

Fig. 7 (case 20).—Glandular portion of nasal mucosa from a woman 70 years of age, who died of pneumonia: *a*, accumulation of normal serous glands with moderate periglandular infiltration; *b*, excretory ducts ensheathed by hyalinized connective tissue; *c*, capillaries ensheathed by thickened, partially hyalinized connective tissue.

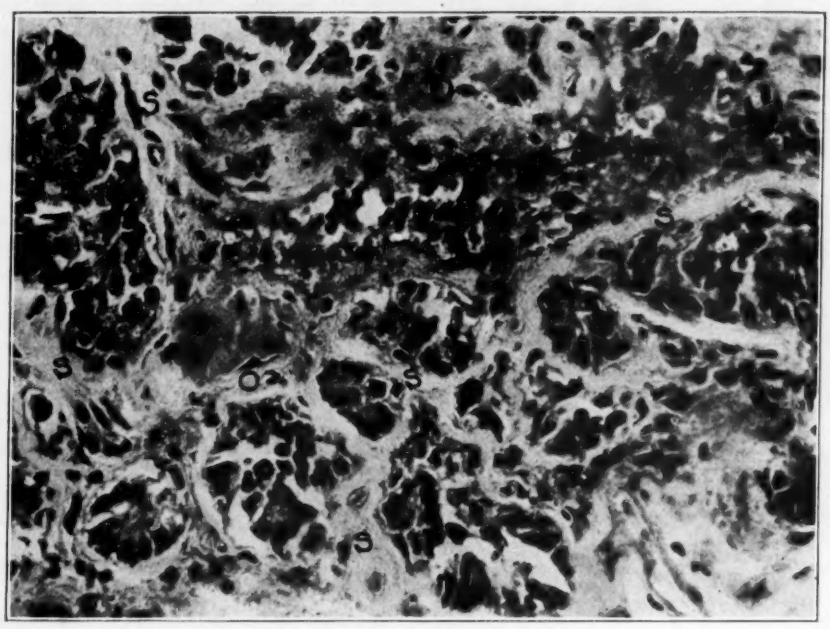

Fig. 8 (case 21).—Glandular portion of nasal mucosa from a man 60 years of age, who died of hepatic cirrhosis; pyelonephritis and degeneration of the myocardium: *o*, pyknocytes (described by H. Brunner and J. W. Wall [Ann. Otol., Rhin. & Laryng. **49**:688 (Sept.) 1940]); *s*, thickened and hyalinized septums between the glands. Note that there are some artificial changes in the specimen due to its preparation.

flammatory process in the mucosa. Therefore, in atrophic rhinitis there are always foci of active inflammation next to the fibrosed areas, there is marked damage to the glands, and there is wide extension of squamous epithelium.

In older persons the fibrosis does not follow a definite inflammatory process but follows degenerative changes involving the lymphoid tissue. Therefore, the fibrosis does not always consist of firm connective tissue but frequently of loose, even edematous tissue. There is only a spotlike destruction of the glands and the squamous epithelium does not extend over large areas. On the contrary, there are large areas which present entirely normal pseudostratified columnar epithelium. To sum up, the mucosa of older persons and the mucosa of patients with atrophic rhinitis resemble each other in certain respects, but pathologically and clinically they cannot be considered identical.

SUMMARY AND CONCLUSIONS

While all types of epithelium were seen in specimens of nasal mucosa from the turbinates of older persons, no definite relation could be established between the age of persons and the type of epithelium.

In contradistinction to the subepithelial layer of younger persons, which is characterized by accumulation of lymphatic tissue, occasionally even forming follicles, the specimens studied seldom showed diffuse accumulation of lymphatic tissue in the subepithelial layer.

In the majority of specimens connective tissue was more abundant than is usually observed in specimens from juvenile persons; the exceptions were those specimens in which the corpus cavernosum was overdeveloped. When the connective tissue was firm, there was frequently marked deposition of hyalin.

Elastic tissue presented marked individual variations as far as quantity is concerned, but there is no known relation between age and development of elastic tissue.

When bone was present in the specimens, osteogenesis was most frequently observed, osteoclasis being seen only occasionally.

The corpus cavernosum did not show any conspicuous signs, although there was a definite variety of the quantitative development. From the observations in 2 cases one is able to conclude that the nasal corpus cavernosum may present hypertrophy in that its blood spaces become increased in number at the expense of the interstitial and subepithelial tissue of the mucosa. Since in both cases there was cirrhosis of the liver, one might think of varicosities in the cavernous tissue of the nose resembling the varicosities often found in the esophagus in cirrhosis of the liver.

The glands were found in various stages of activity. Frequently the excretory ducts of the glands were each surrounded by a thick ring of hyaline tissue even when they were situated in the depths of the lamina propria of the mucosa. Instead of thin septums between the glandular acini there were definitely thickened septums, and the septums even became hyalinized. These septums, through the exertion of pressure on the glands, caused them to degenerate and become atrophic.

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MÉNIÈRE'S SYNDROME

RESULTS OF TREATMENT WITH NICOTINIC ACID IN THE VASOCONSTRICTOR GROUP

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In previous communications[1] evidence has been produced to show: (1) that in cases of idiopathic Ménière's syndrome one of two vascular mechanisms is at work, a primary vasodilator and a primary vasoconstrictor mechanism, either of which can produce the characteristic picture; (2) that these two groups can be differentiated by means of an intradermal test with histamine; (3) that the treatment appropriate to one group is inappropriate and in fact deleterious in the other; (4) that therefore accurate grouping is a prime requisite for effective therapy. Further experience has only served to confirm these conclusions.

The satisfactory results obtained by desensitization to histamine in the primary vasodilator group have already been published.[1b] It is gratifying to be able to report that similar results continue to be obtained and that the improvement in the original cases is maintained.

This paper is concerned with the method and the results of treatment in the primary vasoconstrictor group, that much larger group in which the response to histamine injected intradermally is normal.

THE MATERIAL

The present series comprises 110 cases in which treatment was given for the vasoconstrictor type of Ménière's disease in the three and one-half years from January 1940 to June 30, 1943. It includes 49 cases already reported.[1c] All the patients in the cases under review have been under personal observation, and each has been free of attacks either for six months or for a time longer than the interval which elapsed between the last two attacks of vertigo, whichever of these is the greater. All have the idiopathic syndrome; all have been tested by intradermal injection of histamine and have given a normal response; thus all belong to the histamine-insensitive or primary vasoconstrictor group. All have been treated on similar lines by the method to be described.

PRINCIPLES OF TREATMENT

Two principles are observed in the treatment of patients with Ménière's disease of the vasoconstrictor type. One is to produce a vasodilator effect. The other is to maintain that effect continuously until such time as control is obtained, which may be many months.

Production of the Vasodilator Effect.—Vasodilation can be produced in some degree by a number of vasodilator drugs, but none of the many which I have tried has been found so effective as nicotinic acid. This substance can be given over long periods without harm and without producing tolerance. Moreover, its action is at the periphery of the vascular system on the smallest vessels, as is apparent from the cutaneous flush which follows its administration. This distal effect is the effect wanted, since it is the circulation in the capillaries of the stria vascularis which is believed to be at fault in this condition, at least so far as concerns the aural manifestations.

It may be interpolated here that it is essential to use nicotinic acid, not nicotinic amide. Whereas the two substances are interchangeable as regards their vitamin effect, they are not interchangeable as regards vasodilator effect, which is the effect required here. Nicotinic amide has no vasodilator action. It has been my experience to see many patients who have been treated for Ménière's syndrome with the amide without result and to treat them with the acid with success. I repeat that the acid must be used, not the amide.

The following case may drive home the point. A patient who had responded very well to treatment went to live in another city. He was instructed to continue making occasional injections for a time and was given a prescription to take with him for injectable nicotinic acid should he need it. After a while he came back rather despondent, with a recurrence of attacks, luckily not severe. It turned out that the druggist to whom he had taken his prescription when he had used up the content of the bottle he took

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1. Atkinson, M.: (*a*) Observations on the Etiology and Treatment of Ménière's Syndrome, J. A. M. A. **116**:1753 (April 19) 1941; (*b*) Histamine in the Treatment of Ménière's Syndrome: An Appraisal, ibid. **119**: 4 (May 2) 1942; (*c*) Diagnosis and Treatment of Ménière's Syndrome, Arch. Otolaryng. **37**:40 (Jan.) 1943.

with him from New York was an up-to-date and kindly man. He said, "Why don't you use the new improved flushless compound? Incidentally, I have it in stock, while for the other you will have to wait while I order it." My patient, knowing no better, agreed to the suggestion and was mightily irate when cause and effect were explained to him. That kindly thought had cost him a long journey by train and considerable discomfort.

Maintenance of the Vasodilator Effect.—Only with adequate dosage, long continued, can success in these cases be expected. The dose of nicotinic acid must be worked up to the highest which the patient can tolerate, and this has to be determined for each patient, for there are wide individual variations; it must be kept at this level until symptoms have been brought under control; only then may it be reduced gradually to the minimum necessary to maintain control, and this maintenance dose must be continued for months, perhaps even years.

Moreover, at any moment the threat or the occurrence of a recrudescence of symptoms may be expected and will demand a temporary stepping up of the dosage. The natural history of the condition when left untreated is in most cases a gradual increase in frequency and severity of attacks, at least for a matter of some years. What the treatment advocated here will accomplish is not an abrupt abolition of attacks but rather a gradual diminution of them, as regards both frequency and severity, until eventually complete control is obtained. This must be explained to the patient at the outset of treatment, and he must be warned against discouragement should another attack occur, as almost undoubtedly it will. The patients are few who are relieved completely from the beginning.

From the foregoing considerations it will be evident that the course of treatment advocated here is a prolonged one, demanding patience and persistence on the part of the sufferer and individualized care on the part of the physician. The casual prescribing of a 50 mg. tablet of nicotinic acid to be taken thrice daily is most unlikely to meet the need, particularly as the capacity of the stomach to absorb nicotinic acid seems to vary considerably from time to time even in the same person, at least in one with this syndrome. Yet it is a common experience to encounter a victim of Ménière's disease who has been treated in this way, often for a few weeks only, and because there has been no material change in his condition in that time and under those circumstances, he has been labeled "did not respond to nicotinic acid." The probability is that he never absorbed more than a few milligrams of nicotinic acid during the whole period. By such inadequate methods may sound procedures be discredited.

I would beg of my colleagues who have patients to treat for Ménière's disease that they do not haphazardly try first this method or drug, then that, then another, finally to give up in despair and discard the patient or hand him over to the surgeons. Neither a salt-free diet, nor ammonium chloride, nor histamine, nor nicotinic acid, nor operation is the final answer to the harassed practitioner's prayer. There is no single answer. There is no one "correct" treatment for *all* cases of Ménière's disease. For Ménière's disease is not a disease but a syndrome, the syndrome of the labyrinth, and the cause of the explosion in the labyrinth may be one of several. Only if the operative cause is discovered in the individual case can the appropriate treatment be instituted. It is the old story of effective treatment depending on correct diagnosis. However, if the physician in charge of the patient will make a thorough clinical study of his patient —and he will get more information from a detailed history and a thorough examination than he will from the clinical laboratory, which will help him little if at all—if he will do this and then institute the appropriate treatment and persist with it, he will often be agreeably surprised at the results of his persistence. But he must persist even in the face of initial discouragement, for little or no improvement may be evident until some weeks have passed.

DETAILS OF METHOD

The method which has been found most efficacious has been to start with injections [2] and then, after a period which depends on the response to treatment, gradually to wean the patient from injections to oral medication only. The reason for the advocacy of parenteral therapy is that it has been found in practice that patients who have shown no response to oral therapy will often respond promptly to injections. Major attacks become minor; minor attacks become less frequent and cease; tinnitus and pain in the head subside or disappear. Nicotinic acid, as has been said, is often poorly absorbed from the stomach in cases of Ménière's syndrome of the vasoconstrictor type.

As the individual response to nicotinic acid is variable, the appropriate dose for each patient must be determined with some care. As with a vaccine, the correct dosage is determined by the clinical response. "Experientia docet." The matter is not too difficult if care is taken.

Intravenous Injections.—When it is required to gain control quickly because of the frequency or the severity of the attacks, intravenous therapy is indicated. If

2. The preparation used for the injections, the monoethanolamine salt of nicotinic acid, was supplied for this investigation by Abbott Laboratories, Inc.

time allows, and it usually does, it is wise to start with an initial intramuscular dose of 30 mg. to test the degree of reaction of the patient. With that as a guide, 25 to 35 mg. is given as the first intravenous dose. Treatment is repeated daily or every second day until six to eight doses have been given, increasing the dose by 5 mg. on each occasion to the maximum tolerated, which is usually in the neighborhood of 50 mg., but may be as high as 75 mg. and on rare occasions higher still. All depends on the individual patient. After a few days, oral administration is started in addition; usually 50 mg. is given twice daily on days of injection and thrice daily on the others.

Intramuscular Injections.—Following the course of intravenous injections, a course of intramuscular injections of the maximum dose is started, and these the patient can be taught to give himself in the thigh. If the disease is of the milder type, intramuscular therapy can be used from the start and then must begin at a lower level of dosage and work up as in the case of the intravenous injections. The intramuscular injections are taken daily for one to three months, depending on the control of symptoms, then are gradually diminished in number to five, four, three, two and one a week, and eventually discontinued.

As in the case of intravenous injections, tablets are taken with these injections, 100 mg. or more as necessary on days of injection and 150 mg. or more on other days. A common practice of my own is to order that a 50 mg. tablet be taken after each meal and that a 50 mg. dose be injected intramuscularly before going to bed, but this may well have to be revised upward or downward. There is no fixed routine.

Oral Administration.—After several months of "mixed" therapy, oral treatment alone may be substituted provided that symptoms are under control. Here again the individual maintenance dose has to be found. I have a patient, for instance, who is free of attacks on 250 mg. a day, taken orally, but starts to slip at 200 mg., and has troublesome frontal headache at 300 mg. All cases are not so prettily precise as that.

When determined, the maintenance dose must be continued day in, day out for a period which cannot be foretold but which in any event extends over many months. Perhaps it should be continued for the rest of life. I have patients who after three years of steady treatment start to relapse if they omit their tablets. On the other hand, some have been relieved and have been off treatment for months; others give themselves an occasional injection when they feel that they need it. They learn to tell, by some discomfort in the ear or some mild sense of instability, that the time has come.

A few patients can be treated satisfactorily from the beginning with tablets only. Such are found mostly in the older age group, and their symptoms are mild. But in any case in which a response to oral therapy is not obtained promptly, there should be no hesitation in resorting to parenteral administration.

The age of the patient is a factor to be considered in adjudging dosage. With the elderly and the old patients, in whom arteriosclerosis often complicates the picture, caution is advisable, especially in regard to intravenous injections. I precipitated two severe attacks in an elderly lady by overdosage; on each occasion she was felled to the ground without warning within twenty minutes after an injection.

On the other hand, in the young group, patients in the twenties or early thirties, a considerably higher dosage than average can often be tolerated and may be necessary. It may also produce startlingly good results, as in a man of 34 years who was having daily severe attacks when first seen. He took 75 mg. daily intravenously for two weeks and then maintained a high intramuscular dosage for many weeks. He has now been free from attacks for twelve months; his tinnitus has gone, and his hearing has returned to normal. He still has to take an oral maintenance dose and once in a while an injection (case 2).

RESULTS

The results are shown in table 1. They have been conservatively estimated. As concerns vertigo, no patient has been classed as relieved unless no attack, minor or major, has been experienced for more than the interval between the last two attacks, or for six months, whichever is the greater. It is essential to adopt some such minimum criterion, as only so can any reasonably fair computation of results be made

TABLE 1.—*Results of Treatment with Nicotinic Acid in One Hundred and Ten Cases of Ménière's Syndrome of the Vasoconstrictor Group—Period of Observation, Six Months to Three Years*

	Cases with				Total Number of Cases
	Relief	Improvement	Condition Unchanged	Condition Worse	
Vertigo	42 (38%)	51 (46%)	14 (13%)	3 (3%)	110
	93 = 84%				
Tinnitus	13 (12%)	42 (40%)	45 (42%)	6 (6%)	106*
	55 = 52%				
Deafness	2 (2%)	23 (21%)	80 (73%)	5 (4%)	110
	25 = 23%				

* In four cases tinnitus was noted only at the time of the attack.

in regard to this condition, one of the most characteristic features of which is its tendency to recur. In the improved group are many who have lost their major attacks entirely and regard themselves as relieved but who still have occasional unsteadiness or momentary "flashes" of dizziness. None qualify for this group who continue to have major attacks unless both the frequency and the severity are greatly reduced and the improvement is continuing.

The same conservatism holds for the other symptoms. Relief has to be complete to qualify for the relieved group, improvement definite to qualify for the improved group.

It will be seen that by the means described the vertigo can be relieved or greatly diminished in a large proportion of cases (93, or 84 per cent), the tinnitus in about half the cases (55, or 52 per cent) and the deafness in rather less than a quarter (25, or 22 per cent). Complete relief has been obtained in 38, 12 and 2 per cent, respectively.

In short, inability to relieve the major attacks of vertigo is rare; inability to lessen the deafness is usual; inability to lessen the tinnitus occurs in about half the cases.

In general, the results are satisfactory both to the patient and to the physician. Thus a physician who was a patient writes that "the symptoms had become irregularly frequent" but that after instituting treatment on the lines described they "soon eased and ceased altogether. In the last year I have had only one half-hearted attack and I would not dream of omitting my daily dose."

COMMENT

If these results are compared with those obtained by other medical methods [3] for which adequate figures are available (table 2), it will

TABLE 2.—*Results of Various Medical Treatments for Ménière's Syndrome*

	Period of Observation	Cases	Percentage with Relief of Vertigo	Percentage with Improvement of Vertigo	Deafness	Tinnitus
Mygind and Dederding [3a] (dehydration)	Up to 3 yr.	157	43	52 (95)	17.4	—
Furstenberg and others [3b] (low intake of sodium)	3 mo. to 7 yr.	35	57	26 (83)	9	51
Walsh and Adson [3c] (low intake of sodium)	Up to 4 yr.	152	34	28 (62)	28	"Essentially the same as deafness"
Atkinson (nicotinic acid)	6 mo. to 3 yr.	110	38	46 (84)	23	52

be seen that none of them vary considerably. Indeed, the correspondence as regards relief of vertigo is remarkable; the figures for improvement show a wider spread, perhaps due to a difference in criterion. This close correspondence in results is of considerable interest, since the methods used have been different. It seems to point to an identical basic fault which is being attacked in different ways.

What is this basic fault? According to Mygind and Dederding,[3a] it is a propensity to retain water, wherefore they institute a salt-free diet and limit the intake of fluids. According to Furstenberg[3b] it is retention in the tissues of the sodium ion, wherefore a diet low in sodium content is adopted. I believe that it is an undue permeability of capillary walls, wherefore in the group in which the disease is due to anoxemia from a primary vasospasm, with which group alone this paper is concerned, a capillary vasodilator (nicotinic acid) is employed to increase the oxygen supply and so restore normal capillary function.

On the analogy of a leaking reservoir, the first method seeks to prevent the seepage by reducing the water supply, the second by reducing the avidity of the surrounding terrain for water, the third by repairing the walls. The last is the logical method if it is possible. The results of the treatment advocated in this paper seem to show that in many cases it is.

If the ultimate basic fault is accepted to be an undue permeability of capillary walls manifesting itself particularly in the capillaries of the stria vascularis, though not necessarily confined to them, one has an explanation for many hitherto perplexing features of this condition. It explains why treatment effective in some instances is ineffective in others, since the increased permeability of capillary walls can be due to more than one factor—to anoxemia from vasospasm as in the cases reported here, to undue sensitivity to histamine as in cases previously reported by me,[1b] and to a primary allergic disturbance as reported by Dohlman,[4] by me [1a] and by many others. It can explain, also, many of the general manifestations often associated with attacks of Ménière's disease, such as headache, "fibrositis," vasomotor rhinitis and angioneurotic edema, as pointed out by Mygind and Dederding.[3a]

The postulate of capillary dysfunction will explain, in short, why Ménière's disease is not a disease but a syndrome, and why, moreover, it must be regarded, investigated and treated as a general, not a local, disorder. The familiar triad of vertigo, tinnitus and deafness is only the aural manifestation of a general disturbance.

ILLUSTRATIVE CASES

I have selected 3 cases to illustrate certain points. The first case is a fair average sample. It is a case of moderately severe Ménière's syndrome which demonstrates the virtue of persistence. The second is a case of extremely severe degree to show the spectacular result that can sometimes be obtained. The third illustrates the group of cases in which vertigo can be relieved but other symptoms persist intractably, making life miserable for the sufferer even though he has no more dizzy spells.

3. (*a*) Mygind, S. H., and Dederding, D.: Les syndromes ménièriques, Paris, Presses Universitaires de France, 1934. (*b*) Furstenberg, A. C.; Lashmet, F. H., and Lathrop, F.: Ménière Symptom Complex: Medical Treatment, Ann. Otol., Rhin. & Laryng. **43**:1035 (Dec.) 1934. (*c*) Walsh, M. N., and Adson, A. W.: Ménière's Syndrome: Medical vs. Surgical Treatment, J. A. M. A. **114**:130 (Jan. 13) 1940.

4. Dohlman, G.: Ménièresche Krankheit auf allergischer Basis, Acta oto-laryng. **27**:245, 1939.

I have purposely not included any case of disease in which control was acquired rapidly and maintained easily, or any case in which the result was an out and out failure, since the first teaches little, while the second requires a discussion of failures and their causes too long to enter into here.

CASE 1.—A man aged 39 years, first seen by me on Dec. 1, 1941, had suffered for two years from attacks of objective rotatory vertigo. These were becoming increasingly severe and frequent. When I first saw him he was having three to four attacks daily with an occasional free interval of a week or so. The attacks would last from five minutes to six hours and were accompanied always by nausea and sometimes by vomiting. He had vertical headache all day and every day. There was marked impairment of hearing in the right ear (chart 1 *A*) with constant tinnitus.

He was given twelve intravenous injections (the first eight at daily intervals, the last four at two day intervals, the dose gradually increasing from 30 mg. to 65 mg.). At the same time he was taking tablets (100 mg. up to 300 mg. daily). His acute vertigo was immediately controlled, but he had momentary "flashes" from time to time. Headache was greatly diminished; tinnitus somewhat diminished; the audiogram slightly improved. He was taught to give himself intramuscular injections, 75 mg. daily, and took 200 mg. tablets daily.

He opened the New Year (1942) with two severe spells and a general relapse (no. 1), was given six intravenous injections at two day intervals (75, 90, 100 mg.), at the same time continuing to give himself injections on the other days, and was brought under control until the end of January. Then he again had a relapse (no. 2), and again treatment was stepped up so that by mid-February he was stable again. At the beginning of April he began to reduce the frequency of his intramuscular injections and to inject smaller doses until by May he was taking an injection only occasionally as he needed it. He still took tablets, 300 mg. daily. Headache was mild and occasional, tinnitus slight.

In October 1942 (relapse 3) and again in November (relapse 4) and January 1943 (relapse 5) he had two or three small attacks, and injections were instituted again for a while. Since then until the date of writing (December 1943) he has had no further relapse. He has, however, continued to have occasional "flashes," and when these start to increase in frequency he takes three or four injections and they subside again. He has continued to take tablets regularly, gradually reducing his dose from 300 to 150 mg. a day. When last seen (Dec. 2, 1943) he reported very occasional "flashes" but no vertigo; hearing was almost normal (chart 1 *D*); tinnitus was mild—some days there was none at all; headache was noted about once a week for ten minutes or so on first getting up in the morning. This is regarded by both the patient and myself as a satisfactory outcome of a serious disturbance.

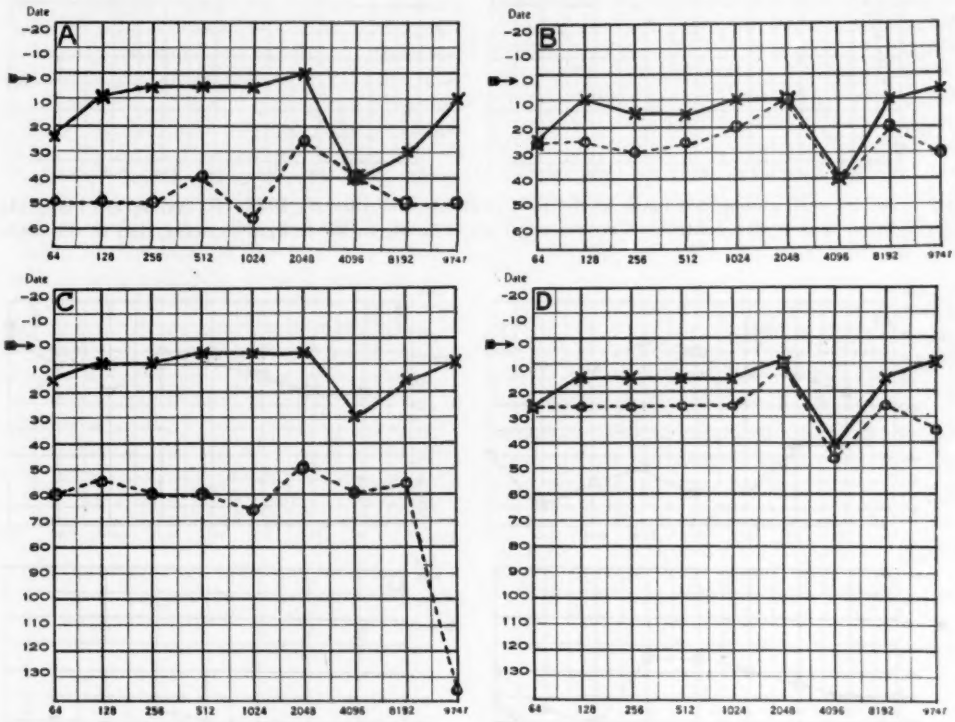

Chart 1 (case 1).—*A*, audiogram made at the first examination Dec. 1, 1941. *B*, audiogram made after treatment, June 18, 1942. *C*, audiogram made during a relapse, Nov. 19, 1942. *D*, audiogram made after control had been reestablished, Dec. 2, 1943. Crosses represent hearing in the left ear; circles, that in the right ear.

CASE 2.—A man aged 34 years, first seen on June 15, 1942, had his first attack of Ménière's syndrome four years previously. After a free interval of two years he had another, followed by several more during the winter of 1940-1941. Histamine injected intravenously "worked wonders," and he was free of attacks until three weeks before being seen by me. Then he

had a severe attack which "knocked him out of a chair" and lasted for twelve hours, after which he had daily attacks which seemed to be made worse by histamine, which was administered on seven occasions. When first seen by me, he had been continuously dizzy for several days, with periods of exacerbation in which he had acute vertigo, great impairment of hearing in the right ear and severe tinnitus. He was vomiting at frequent intervals and was severely ill and dehydrated.

Nicotinic acid was given intravenously daily, the doses starting with 50 mg. and rapidly increasing to 90 mg. This controlled the vertigo immediately, so that he had only one more severe attack, four days later. With general care his condition rapidly improved, and after fifteen daily intravenous injections he was taught to give himself daily intramuscular injections. After a month of these (July 1942) his hearing had improved, his tinnitus had ceased and he had experienced only one mild attack. The dose was gradually diminished during August and September.

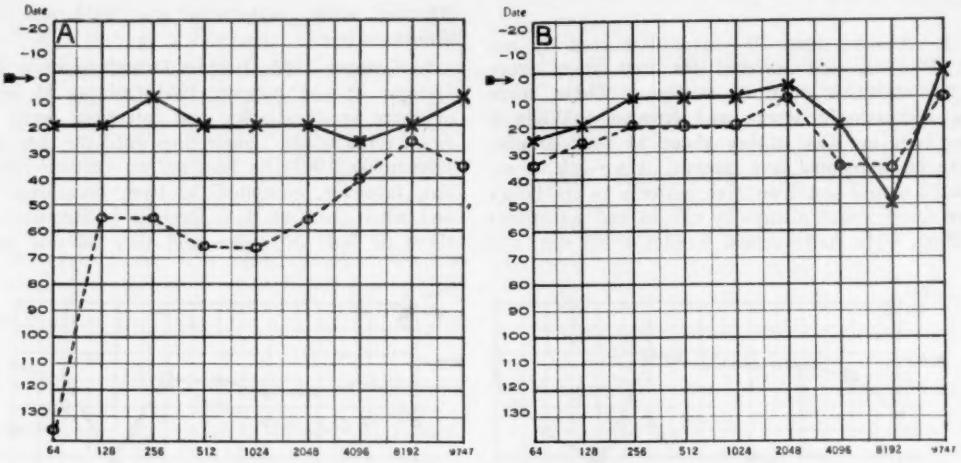

Chart 2 (case 2).—*A*, audiogram made at the first examination, July 30, 1942. *B*, audiogram made Dec. 2, 1943, when the condition was under control. Crosses represent hearing in the left ear; circles, that in the right ear.

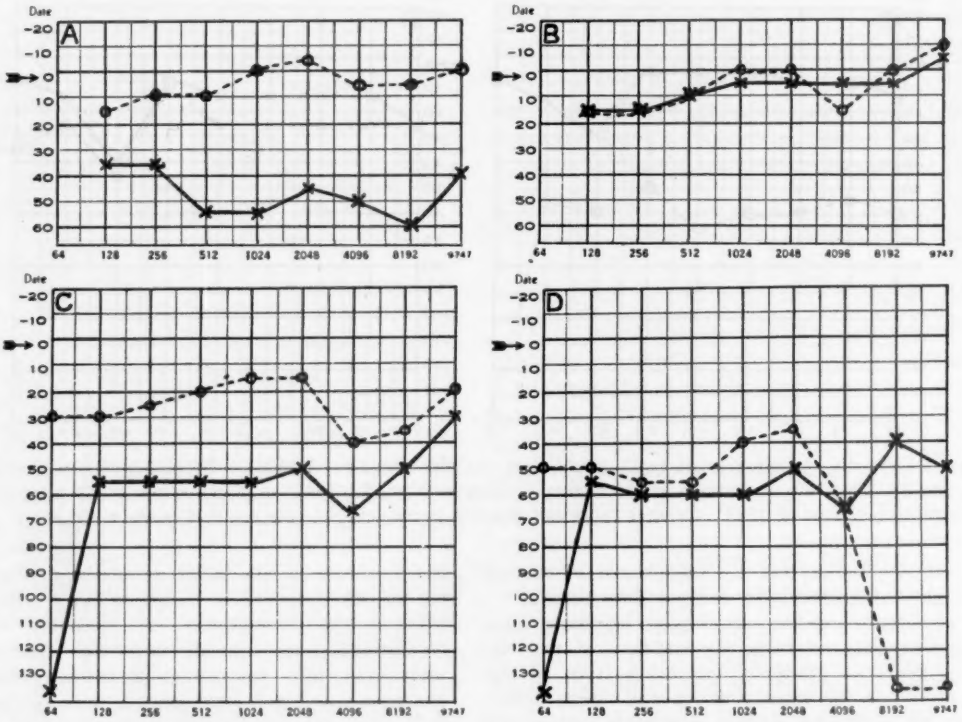

Chart 3 (case 3).—*A*, audiogram made at the first examination, April 25, 1939. *B*, audiogram made after treatment, Sept. 17, 1940. *C*, audiogram made on recurrence, May 4, 1942. *D*, audiogram made after control had been lost, Sept. 8, 1942. Crosses represent hearing in the left ear; circles, that in the right ear.

In October 1942 he had a mild relapse—one mild attack and frequent unsteadiness, with tinnitus again and hearing impaired. The dosage was stepped up and control again rapidly achieved. In March 1943 he again had a mild relapse, which was again controlled by increasing the dose. From mid-May until December

1943, when he was last seen, he had experienced no further attacks and was almost free of tinnitus, and his hearing was practically normal (chart 2). He has learned how to take care of himself. If his "head goes bad," evidenced by varying deafness and tinnitus, he gives himself 100 mg. of nicotinic acid intramuscularly, after which, he says, his head clears at once. He takes 100 to 300 mg. by mouth daily. He finds that 100 mg. taken on an empty stomach produces a good flush and a sense of increased well-being, so that he adopts this treatment in place of injection when his head "goes only mildly bad." Most of the time, however, he feels perfectly well.

CASE 3.—A man aged 46 years, first seen on Nov. 29, 1939, had suffered for twenty-six years from impairment of hearing in the left ear from no known cause. Sixteen years before being seen by me he had his first attack of vertigo. After that he had no trouble other than the impairment of hearing until January 1939, when he had another attack, followed by four or five more between then and coming for treatment. During this time he experienced continuous tinnitus, often loud and disturbing, so that at the time of his first examination he had the complete syndrome.

He was given nicotinic acid, 150 mg. daily by mouth —this was in the early days before it was realized that injections gave much better results—and during the next five months he had three severe attacks, one of which felled him. During this period his tinnitus ceased occasionally, but most of the time was troublesome. He was taught to give himself intramuscular injections, increasing the dose from 20 mg. to 35 mg. daily (April 1940). From then until mid-August he had no further vertigo, tinnitus had ceased and hearing in the affected ear had surprisingly returned to normal. Then for six weeks until the end of September 1940, he had a relapse, with frequent mild vertigo, variable tinnitus and diminution in hearing. The dose of nicotinic acid given intramuscularly was raised to 50 mg. daily for a month, which controlled his symptoms (intravenous injections would probably have done it much more quickly).

Another relapse occurred in December 1940, while he was taking nicotinic acid by mouth only, and was controlled by further injections. Again he was given oral medication, and again in February 1941 he had premonitions of an attack in a sense of ill-being and increased tinnitus. He was given an injection of an acetylcholine salt, 0.1 Gm., following which his tinnitus promptly subsided and the next day he felt much better. He continued to take nicotinic acid by mouth and was well until April 1942.

In May 1942 his good ear (right) started to be affected (chart 3 *C*). He noticed tinnitus and some impairment of hearing, and during the next three months he had several attacks, some of them severe, with troublesome tinnitus in both ears, and hearing was greatly impaired bilaterally. Nicotinic acid given intravenously in doses up to 100 mg. eventually effected control. His attacks ceased, and he has had none since except for one knock-down attack after taking amphetamine—good corroborative evidence of the vasospastic nature of the condition. Hearing on both sides is now equally impaired, and it appears that balance has been effected by an equal involvement of both sides. Tinnitus is variable, as is the hearing defect, but in general is very disturbing. Moreover, it has changed its character. The low roaring tinnitus of which he complained when first seen has long ceased but has given place to a high-pitched whistle which no medication alters. It disturbs his sleep and makes him miserable. The result must be considered a failure. His attacks of vertigo have ceased, possibly as a result of treatment, and for this he is thankful, but he still is an unhappy man because of the exceedingly troublesome tinnitus.

It is believed that in cases of Ménière's syndrome belonging to the primary vasconstrictor group the disturbance is due to anoxemia of the labyrinth caused by vasospasm and that the treatment therefore logically calls for a vasodilator drug. In a series of 110 cases the patients were treated medicinally exclusively with nicotinic acid, by a method described in this report. The attacks of vertigo were relieved or greatly modified in 84 per cent of the cases.

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HEREDITARY HEMORRHAGIC TELANGIECTASIA (OSLER'S DISEASE)

A REVIEW OF THE LITERATURE AND REPORT OF CASES

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Hereditary hemorrhagic telangiectasia is a rare disease, probably due to mesenchymal dysplasia. It is characterized by the presence of multiple acquired angiomas or telangiectases of varying distribution and number with a marked tendency to bleed spontaneously or from slight trauma. The disease is not sex bound. It is transmitted as a dominant characteristic. The initial symptom usually consists of abnormally profuse epistaxis beginning about puberty. This is followed by the development of multiple telangiectasia of the skin and mucous membranes from the age of 25 to 35. Hemorrhage from the nasal mucosa is most frequent, and all symptoms tend to reach their greatest severity during the fourth decade. The average mortality rate is 4 per cent.

The lesions are most commonly found in the nasal mucosa, the skin of the face, the buccal mucosa, the lips, the tongue, the floor of the mouth, the scalp, the ears, the conjunctivas and the finger tips. Other common sites are the ear drums, the palate, the pharynx, the larynx, the trachea, the esophagus, the stomach, the intestines, the bladder, the uterus and the urethra. The lesions have also been described in the brain, the meninges, the liver, the spleen and the kidneys. They vary in color from red to purple and in size and form from pinpoint spots to the larger nodular forms and the large "spider form," or nevus araneus. They blanch on pressure, unless a hemorrhage has taken place recently. The blood is normal.

Microscopically the lesion usually shows an increased number of dilated vessels with greatly thinned walls. The tissues covering the vessels are usually thinned, which permits hemorrhage to occur from trivial causes. Thrombosis is frequent and probably explains the tendency of the lesions to disappear spontaneously, while new ones arise elsewhere.

In differential diagnosis one must consider the telangiectases due to syphilis, senility, pregnancy and lead poisoning and differentiate the disease also from leukemia, aleukemia, aplastic anemia, thrombopenic purpura hemorrhagica, hemophilia, cirrhosis of the liver, cancer, persistent macular eruption, familial hemorrhagic purpura, Banti's, Gaucher's and Hodgkin's diseases and Sturge-Weber disease.

Treatment consists of various measures adopted to achieve immediate hemostasis, together with transfusions if necessary. Permanent cures have been reported following various types of cauterization and irradiation therapy. It has been reported that the type 4 (Moss) blood group is intolerant of transfusions in the presence of splenohepatomegaly.

Goldstein estimated that about 120 affected families, including 700 members, had been reported up to 1933. On that basis probably 175 affected families, including 1,000 members have been recorded to date. In only a few instances has the disease been traced through six generations, although there are numerous reports dealing with its transmission through three and four generations. This probably indicates self limitation of the hereditary transmission of the disease.

The disease is usually held to be hereditary, but it seems that at least 20 per cent of the recorded cases have lacked a family history of the occurrence of the disease and were not examples of atavism. These are probably actual cases of Osler's disease in which the hereditary factor is lacking. It cannot be definitely stated whether or not in such circumstances the patients are able to transmit the disease to their progeny.

REVIEW OF THE LITERATURE: 1933-1944

Since Houser's [1] review of the literature, in 1934, many new papers have appeared. He reported an affected family with a mortality rate of 27.2 per cent, compared with the average of 4 per cent. He employed chromic acid successfully and noted the appearance of satellite lesions following the destruction of the original angiomas.

Aubertin, Levy and Baclesse [2] discussed the role of heredity. They found a 30 per cent incidence of the angiomas among the members of an affected family. The telangiectases in

1. Houser, K. M.: Hereditary Hemorrhagic Telangiectasia, Ann. Otol., Rhin. & Laryng. **43**:731-738 (Sept.) 1934.

2. Aubertin, C.; Levy, R., and Baclesse: L'angiomatose hemorragique familiale (maladie de Rendu-Osler), Presse méd. **41**:185-188 (Feb.) 1933.

about 50 per cent of these affected members were "formes sans hemorragies." Isolated, nonhereditary or atavistic telangiectases were recognized as "formes veritablement sporadiques."

Teahan [3] and Alban [4] reported cases occurring in families affected by the disease for six generations. This finding is of such extreme rarity as to indicate that the hereditary transmission of the disease is to some degree self limited.

Goldstein [5] said the disease was hereditary and as such was incurable, owing to its nature.

Fingerland and Janousek [6] recorded observations on an affected family. They noted the extreme severity of symptoms in persons with dark skin and hair.

Figi and Watkins [7] stated that at the Mayo Clinic the diagnosis had been made in 20 cases in twenty years. Six cases lacked a positive family history.

Goldstein [8] indicated a possible relationship to Recklinghausen's disease and to nevus anemicus. He quoted Springels, Fischer, Stein, Naegeli, Weber, Cushing and Bailey. Gjessing's patient had conjunctival bleeding, and Moller in 1930 reported familial angiomatosis of the retina and the cerebellum.

A possible relationship to Hippel's, Lindau's, Sturge-Weber and Bourneville's diseases was postulated by Ullmann,[9] Kufs,[10] Junius,[11] Michael and Levin,[12] Ironside,[13] Louis-Bar [14] and Cordes and Hogan.[15]

Madden [16] presented a patient whose brother died of epilepsy, suggesting intracranial angiomas.

Muende's [17] patient presented fibroangiomas instead of the simple angiomas observed in the other members of the family.

Goldstein [18] reported cerebral hemorrhage from hereditary telangiectasia.

Kosiner's [19] patient presented associated hereditary branchyphalangia and diabetes.

Netherton's [20] patient had associated Raynaud's disease with calcium deposits in the fingers.

Kugelmass [21] reported the disease as affecting only one of twins.

In Milbradt's [22] case there was accompanying diffuse atypical scleroderma and hepatic disease. This would indicate widespread mesenchymal dysplasia.

Harding [23] recorded a case with associated hemiatrophy, syphilis and tuberculosis. Hepatomegaly was also present.

Van Bogaert [24] added 2 cases with and 2 cases without hepatosplenomegaly.

Davis [25] reported a case in which familial hemorrhagic purpura was an associated condition.

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6. Fingerland, A., and Janousek, B.: Hereditary Hemorrhagic Telangiectasia (Osler's Disease), Arch. f. Dermat. u. Syph. **178**:54-64, 1938.

7. Figi, F. A., and Watkins, C. H.: Hereditary Hemorrhagic Telangiectasia, Ann. Otol., Rhin. & Laryng. **52**:330-341 (June) 1943.

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18. Goldstein, H. I.: Heredofamilial Angiomatosis (Telangiectasia) with Recurring Hemorrhages, Internat. Clin. **2**:43-56 (June) 1934.

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21. Kugelmass, I. N.: Hereditary Hemorrhagic Telangiectasis, J. A. M. A. **102**:287-291 (Jan. 27) 1934.

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25. Davis, E.: Hereditary Familial Purpura Simplex, Lancet **2**:1110-1114 (Nov. 25) 1939.

Milbradt's, Kosiner's, Muende's and Netherton's cases, among others, indicate a widespread mesenchymal dysplasia not limited to the vascular elements, as do many of the other cases reported.

Cases of telangiectasia probably due to syphilis were reported by Bankoff,[26] Combes [27] and Michelson.[28] These cases were reported as possible instances of Osler's disease, but the evidence favors a different diagnosis.

Obermayer and Becker [29] presented cases of telangiectasis due to pregnancy. Improvement resulted from treatment with thorium X.

Zeisler [30] reported telangiectasia associated with both syphilis and pregnancy.

McDonough, Dry and Roth [31] recorded an atypical case lacking a positive history of heredity and the characteristic symptoms. Probably the patient's weakness and hepatomegaly were due to the decompensated cardiac condition. The diagnosis of Osler's disease was probably incorrect.

Cases with gastric involvement were recorded by Renshaw,[32] who on gastroscopy found eight mucosal angiomas; by Griggs and Baker,[33] who reported 3 cases, and by Stellar.[34] Stellar's patients required eight transfusions, and reactions did not occur even though the patient had blood of type 4 (Moss) and hepatomegaly. One of Grigg's patients had splenomegaly and another had splenohepatomegaly and a transfusion reaction.

Meikle [35] and Renshaw [32] reported angiomas of the larynx. Gerlings and Polak [36] diagnosed tracheobronchial lesions. Cordier [37] reported hemoptysis in a typical case.

Scheer's [38] patient was a 9 year old boy with the lesions limited to one side of the face. There was no family history of the disease.

Splenomegaly or splenohepatomegaly was present in 8 cases, with report of only one transfusion reaction. The patient had blood of type 4 (Moss) and had the disease in a severe form.

Hematuria was reported by Blum [39] and by Keller.[40] Keller's case occurred in childhood.

Weber [41] described unusual pulsating stellate telangiectases occurring in a case of hereditary disease. This would indicate involvement of arterial vessels of rather large caliber.

Pillsbury [42] recorded a case complicated by cardiac decompensation. The patient was anemic and had splenohepatomegaly.

Typical cases were reported by Yde and Olesen,[43] Bloom,[44] Combes,[45] Hottenroth,[46] Halloran,[47] Raaschou,[48] Theorin,[49] Földváry,[50] Guy and Amshel,[51] Madden [52] and Rulison.[53]

26. Bankoff, G.: Pathology and Therapy of Essential Telangiectases, München. med. Wchnschr. **80**:2035-2037 (Dec. 29) 1933.

27. Combes, F. C.: Multiple Hereditary Telangiectasia (Osler's Disease) and Cardiovascular Syphilis, Arch. Dermat. & Syph. **44**:114-115 (July) 1941.

28. Michelson, H. E.: Hereditary Hemorrhagic Telangiectasia, Arch. Dermat. & Syph. **36**:241 (July) 1937.

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30. Zeisler, E. P.: Telangiectasia Associated with Syphilis and Pregnancy, Arch. Dermat. & Syph. **5**:781 (June) 1922.

31. McDonough, F. E.; Dry, T. J., and Roth, G. M.: Hereditary Telangiectasia with Visceral Involvement: Special Studies of Skin Temperature; Report of a Case, Proc. Staff Meet., Mayo Clin. **15**:593-604 (Sept. 18) 1940.

32. Renshaw, J. F.: Multiple Hemorrhagic Telangiectasia with Special Reference to Gastroscopic Appearance, Cleveland Clin. Quart. **6**:226-230 (July) 1939.

33. Griggs, D. E., and Baker, M. Q.: Hereditary Hemorrhagic Telangiectasia with Gastro-Intestinal Bleeding, Am. J. Digest. Dis. **8**:344-346 (Sept.) 1941.

34. Stellar, L. I.: Hereditary Telangiectasia: Report of a Case, New England J. Med. **226**:336-338 (Feb. 26) 1942.

35. Meikle, G. J.: Case of Hereditary Telangiectasia, Lancet **2**:863-864 (Oct. 14) 1933.

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38. Scheer, M.: A Case for Diagnosis (Hereditary Familial Telangiectasia), Arch. Dermat. & Syph. **41**: 1189 (June) 1940.

39. Blum, V.: Familial Essential Hematuria and Its Association with Osler's Disease, Med. Klin. **32**:1254-1255 (Sept. 11) 1936.

40. Keller, W.: Hematuria in Childhood: A Case of Probable Telangiectasia Hemorrhagica Hereditaria, Monatschr. f. Kinderh. **79**:376-381, 1939.

41. Weber, F. P.: Hemorrhagic Hereditary Telangiectasia of Osler Type, with Multiple Pulsating Stellate Telangiectases, Brit. J. Dermat. **48**:182 (April) 1936.

42. Pillsbury, D. M.: Multiple Hereditary Telangiectasia (Rendu-Weber-Osler Syndrome), Arch. Dermat. & Syph. **32**:145-146 (July) 1935.

43. Yde, A., and Olesen, M.: Hereditary Angiomatosis (Osler's Disease) in Two Danish Families, Hospitalstid. **77**:1010-1023 (Sept. 18) 1934.

44. Bloom, D.: Osler's Disease (Hereditary Familial Telangiectasia), Arch. Dermat. & Syph. **37**:678-679 (April) 1938.

45. Combes, F. C.: Hereditary Hemorrhagic Telangiectasia, Arch. Dermat. & Syph. **39**:754 (April) 1939.

46. Hottenroth, H.: Contribution to Osler's Disease, Arch. f. Dermat. u. Syph. **178**:582-592, 1939.

47. Halloran, C.: Hereditary Hemorrhagic Telangiectasia, Arch. Dermat. & Syph. **45**:175 (Jan.) 1942.

48. Raaschou, F.: Hereditary Hemorrhagic Telangiectasia (Rendu-Osler) with a Genealogic Table, abstracted, J. A. M. A. **118**:258 (Jan. 17) 1942.

49. Theorin, S.: Eine Familie aus Norrland mit Morbus Rendu-Osler, Acta med. Scandinav., 1941, supp. 123, p. 268.

Figi and Watkins,[7] Houser [1] and Kindler [54] all noted the development of satellite angiomas adjoining the former sites of lesions destroyed by treatment. This seems to indicate that various forms of trauma stimulate the formation of new angiomas and indicates a neoplastic rather than angiectatic origin of the blood vessel tumors.

Lynch [55] found elastic tissue present in fetal blood vessels at the fifth and sixth months. If the lesions of Osler's disease are neoplastic, this may partly account for the absence of elastic fibers.

The microscopic appearance of the cutaneous lesions was studied by Pardo-Castello and Farinas,[56] Fingerland and Janousek,[6] Neumark,[57] Ullmann,[58] Ormsby and Montgomery.[59]

Fingerland described thickening of the walls of the veins with resultant diminution of their lumens and felt that this caused elevation of intracapillary pressure and dilatation.

Ormsby and Montgomery described definite formation of new blood vessels with dilation.

In addition to the degenerative changes in connective tissue, Neumark and Ullmann noted vascular dilatation and numerous newly formed vascular buds consisting of cellular bands which were composed of cells with round or oval nuclei (angioblasts), lying among incompletely formed blood vessels. In an earlier paper Ullmann quoted Billroth, of Vienna, as being of the opinion that the telangiectases are neoplastic. Ullmann described newly formed pathologic capillary blood spaces whose nuclei showed an increase in number and a definite chromatin structure.

Lewis [61] described the pathologic aspects of angiomatosis retinae and discussed the differential diagnosis.

Biomicroscopic studies by Martinez (cited by Pardo-Castello and Farinas [56]), Bommer [62] and McDonough, Dry and Roth [81] revealed an increase in the number of capillaries of the skin. They were dilated, elongated, tortuous, and presented localized aneurysmal dilatations ending in convoluted loops or arches.

Thorium X has been successfully used in treatment by Obermayer and Becker.[29]

Kindler [54] recommended an extensive bilateral window resection of the septal mucosa.

O'Kane [63] injected a 5 per cent solution of quinine hydrochloride and ethyl carbamate into the adjacent anesthetized tissues with good results. Biegeleisen [64] and Watson and McCarthy [65] injected sodium morrhuate into the lumens of the vessels, using a microinjection technic.

Sterman and Scal [66] successfully employed radium, but Figi and Watkins,[7] Houser,[1] Peck [67] and Ingels [68] have condemned its use, as it predisposes to even more severe bleeding, due to the resultant friability of the tissues.

Houser [1] employed chromic acid as a caustic, while Figi and Watkins [7] obtained extremely gratifying results from electrocoagulation. Rulison [53] also successfully treated the angiomas with electrocoagulation.

Figi and Watkins [7] have recommended temporary hemostasis with use of the Cooper Rose

50. Földváry, F.: Hereditary Hemorrhagic Telangiectasia, Magyar orvosi arch. **34**:230-237, 1933.

51. Guy, W. H., and Amshel, F.: Familial Telangiectasia, Arch. Dermat. & Syph. **29**:778 (May) 1934.

52. Madden, J. F.: Hereditary Hemorrhagic Telangiectasia, Arch. Dermat. & Syph. **36**:675 (Sept.) 1937.

53. Rulison, R. H.: Multiple Hereditary Hemorrhagic Telangiectasia, Arch. Dermat. & Syph. **34**:522-523 (Sept.) 1936.

54. Kindler, W.: Epistaxis in Angiomatosis (Osler's Disease), Arch. f. Ohren-, Nasen- u. Kehlkopfh. **143**: 236-240, 1937.

55. Lynch, F. W.: Elastic Tissue in Fetal Skin, Arch. Dermat. & Syph. **29**:57-79 (Jan.) 1934.

56. Pardo-Castello, V., and Farinas, E. P.: Hereditary Multiple Telangiectasia, Arch. Dermat. & Syph. **39**:1025-1034 (June) 1939.

57. Neumark: La maladie d'Osler, in Deliberationes Congressus Dermatologorum Internationalis, Leipzig, Johann Ambrosius Barth, 1936, vol. 2, p. 746.

58. Ullmann, K.: Angiomatosis (Morbus Osler); Ist sie eine Blut- oder Gefasserkrankung? in Deliberationes Congressus Dermatologorum Internationalis, Leipzig, Johann Ambrosius Barth, 1936, vol. 2, p. 743.

59. Ormsby, O. S., and Montgomery, H.: Diseases of the Skin, ed. 6, Philadelphia, Lea & Febiger, 1943.

60. Footnote deleted by the author.

61. Lewis, P. M.: Angiomatosis Retinae, Memphis M. J. **18**:146-150 (Oct.) 1943.

62. Bommer, S.: Microscopic Study of Capillaries in Hereditary Progressive Telangiectasis, Dermat. Wchnschr. **98**:201-210 (Feb. 17) 1934.

63. O'Kane, G. H.: Hereditary Multiple Telangiectases with Epistaxis, J. A. M. A. **111**:242-244 (July 16) 1938.

64. Biegeleisen, H. I.: Telangiectases of the Nose: Treatment by Micro-Injection of a Sclerosing Fluid, Ann. Otol., Rhin. & Laryng. **45**:416-419 (June) 1936.

65. Watson, W. L., and McCarthy, W. D.: Blood and Lymph-Vessel Tumors: One Thousand and Fifty-Six Cases, Surg., Gynec. & Obst. **71**:569-588 (Nov.) 1940.

66. Sterman, M. M., and Scal, J. C.: Familial Telangiectasia with Recurring Epistaxis Successfully Treated with Radium, New York State J. Med. **37**:287-292 (Feb. 1) 1937.

67. (*a*) Peck, S. M., and Rosenthal, N.: Effect of Moccasin Snake Venom (Ancistrodon Piscivorus) in Hemorrhagic Conditions, J. A. M. A. **104**:1066-1070 (March 30) 1935. (*b*) Peck, S. M.: Osler's Hereditary Familial Telangiectases, Arch. Dermat. & Syph. **34**: 1060 (Dec.) 1936.

68. Ingels, A. E.: Hereditary Hemorrhagic Telangiectasia, Arch. Dermat. & Syph. **41**:986-987 (May) 1940.

plug of Hurst and Plummer. This is a small thin rubber bag which is inserted into the nose and inflated.

Peck and Rosenthal [67a] introduced the use of moccasin venom and have recorded good results. Figi and Watkins [7] reported poor results from this form of therapy. Ingels,[68] Weiss [69] and Storey and Akamatsu reported good results from the use of moccasin venom. The venom has no direct effect on the blood and does not reduce coagulation time. Its action is probably limited to the capillary endothelium. This would explain the disappearance of some lesions as reported by Peck.

Cipollaro [70] successfully treated telangiectases with electrolysis, using the negative pole of a galvanic current with an amperage of 0.25 to 2.0 milliamperes for one minute. The needle was inserted in one or more places per lesion, depending on its size.

Fingerland [6] used solid carbon dioxide with good results, as did Bankoff,[20] who also used roentgen rays.

Vitamin K was mentioned by Figi and Watkins.[7]

Irradiation with high voltage roentgen rays was effective for hemangiomas in the hands of Spencer as quoted by Weaver.[71] Spencer stated that radioresistance increased with the age of the patient.

Newcomet,[72] in discussing irradiation of hemangiomas, said that the results of treatment cannot be finally determined for several years. This agrees with my own experience with roentgen therapy for Osler's disease.

Molesworth [73] advised the early treatment of hemangioma by irradiation because of great radiosensitivity of the hemangioma at this stage of its growth.

Figi and Watkins [7] and others irradiated the spleen.

Hare [74] said that in administering large doses of roentgen rays no more than 100 r per portal should be given at one time.

Quick [75] quoted Hurst, Hicks and Knox, Mackay and McKenty, Paul, and Sterman and Scal and said that the most favorable results were obtained with radium.

Weiss [69] found that radium gave only temporary benefit and used snake venom.

Templeton [76] employed electrodesiccation with good results.

REPORT OF CASES

CASE 1.—Miss F. J., aged 58, was first seen during August 1941. Severe epistaxis and telangiectases had developed when she was 4 years of age. During her early teens the lesions and the symptoms had greatly increased in number and severity. There was a family history of the disease. The affected relatives included the paternal grandmother, the patient's father, her only sister and one of her two brothers—those with the patient herself making 5 in three generations. Extremely numerous bright red nodular lesions and a few spider nevi were present on the nasal septum, the floor of the nose and the lateral nasal wall. A few small lesions were present on the tongue and the buccal mucosa. Lesions of the skin were absent. Weakness due to anemia from epistaxis was a frequent occurrence. A correct diagnosis had not been made previously. Vague discomfort in the right upper quadrant of the abdomen had been noted for many years. There was splenohepatomegaly Roentgen studies of the gastrointestinal tract, the kidneys and the gallbladder had given negative results. Two uterine suspensions, an oophorectomy and an appendectomy had been performed, without relief. Long-continued treatment with chemical caustics and electrocoagulation of the septal lesions had resulted in marked atrophy and epithelial metaplasia.

Roentgen therapy of the "intermediate" type was begun during October 1941. Nine treatments were given during a one year period. The total dose was 1,000 r, given at 140 kilovolts, through a filter of 0.25 mm. of copper and 1 mm. of aluminum, at a distance of 25 to 50 cm. For individual treatments the dose varied from 100 to 125 r. The subsequent course of the disease indicated slow but definite improvement. During the six month period following the termination of roentgen therapy, the epistaxis gradually diminished. The patient was free from symptoms during the subsequent six months. This had never before occurred spontaneously. Recently there have been several mild attacks of epistaxis, which did not require medical attention. One year after the roentgen therapy there were fewer angiomas on the lateral wall and the floor of the nose. The septal lesions showed no macroscopic alterations but were markedly less prone to bleed. It is certainly permissible to ascribe this improvement to the roentgen therapy. The slow amelioration of the symptoms is entirely compatible with the known radioresistance of angiomas in the adult.

No cutaneous telangiectases have appeared as a result of the roentgen treatment. If indicated, roentgen therapy will be reinstituted up to the point of tolerance. It is the intention to employ this lengthy method of

69. Weiss, J. A.: Radium Therapy for Recurrent Epistaxis in Hereditary Hemorrhagic Telangiectasia, Laryngoscope **48**:865-869 (Dec.) 1938.

70. Cipollaro, A. C.: Electrolysis, J. A. M. A. **111**: 2488-2491 (Dec. 31) 1938.

71. Weaver, D. F.: Three Unusual Cases of Hemangioma, Ann. Otol., Rhin. & Laryng. **52**:507-515 (June) 1943.

72. Newcomet, W. S.: Treatment of Hemangioma, Am. J. Roentgenol. **39**:470 (March) 1937.

73. Molesworth, E. H.: Importance of Early Treatment of Vascular Naevi, M. J. Australia **2**:217 (Aug. 12) 1933.

74. Hare, H. F.: Problems of Radiation Therapy, Lahey Clin. Bull. **3**:167-173 (Oct.) 1943.

75. Quick, A. J.: The Hemorrhagic Diseases and the Physiology of Hemostasis, Springfield, Ill., Charles C Thomas, Publisher, 1942.

76. Templeton, H. J.: Hereditary Hemorrhagic Telangiectasia, Arch. Dermat. & Syph. **38**:498-499 (Sept.) 1938.

therapy only in cases of severe disease not amenable to local therapy.

Local therapy is necessary while the effects of the roentgen therapy are developing.

This is the only patient whom I have had the opportunity to treat with a prolonged course of small doses of roentgen rays by the "intermediate" method. This method avoids the use of single large doses with their resultant necrotizing or devitalizing effects.

CASE 2.—Miss L. J., aged 55, was first seen in April 1942. She is the younger sister of the patient described in case 1. Epistaxis and telangiectasis had begun when she was 4, but her lesions were fewer and her symptoms milder than her sister's, and treatment was rarely required. A few bright red nodular lesions were present on the septum, the inferior turbinates, the tongue and the buccal mucosa. Cutaneous lesions were absent. It was felt that roentgen therapy was not advisable in the absence of serious clinical symptoms.

CASE 3.—Mr. E. D., aged 60, was first seen in May 1942. There was no family history of the disease, so its occurrence in the patient was either atavistic or nonhereditary. Telangiectases and epistaxis were first noticed by him at the age of 40. Later, as the lesions continued to develop, oral hemorrhages occurred. At the age of 50 he had an attack of spontaneous hematuria.

Examination revealed bright red nodular lesions on the nasal septum, the floor of the nose, the floor of the mouth, the tongue, the hard palate and scattered over the face.

The epistaxis had recently been attributed to hypertension, but the hemorrhages had long antedated the elevation of the blood pressure.

Cauterization with trichloroacetic acid has controlled the hemorrhage, so roentgen therapy has not been used.

It is highly probable that telangiectatic lesions are present in the urethra or the bladder.

CASE 4.—Mr. F. A., aged 54, was first seen in October 1943. There was no family history of the disease. Telangiectases and profuse epistaxis first appeared in the patient at the age of 42. Bright red nodular lesions were found on the septal mucosa, the tongue and the buccal mucosa, and red flattened lesions were present on the face, the lips and the gums. The labial and gingival angiomas were especially large. Profuse spontaneous hemorrhage from the nose and gums had necessitated two transfusions in the past. A correct diagnosis had never been made previously. Chemical cauterization was without permanent effect, so roentgen therapy was advised but has not yet been begun.

CASE 5.—Mr. W. H., aged 42, was first seen in December 1943, when he requested treatment for an earache. The presence of typical angiomas on the ear drum and the face led to an investigation and the eventual diagnosis of Osler's disease. Lesions were found on the ear drums, the nasal septum, the vocal cords, the palpebral conjunctivas, the lips, the face, the trunk and the finger tips. The conjunctival lesions were spider angiomas and the others papular. The liver and the spleen were not enlarged.

Telangiectasia and epistaxis began in early childhood. Bleeding had also occurred from the finger tips and the lips, but the symptoms were always relatively mild. The patient had noted infrequent mild hematuria, hemoptysis, hematemesis and rectal bleeding. The angiomas were not always permanent. The older lesions occasionally would "turn yellow and fade away." The appearance of new lesions was constant during earlier years.

The family history shows six consecutive generations to have been affected. The disease existed in a severe form in the patient's great great grandfather, great grandfather, grandfather, father and one uncle. The great great grandfather died from hemorrhage. The symptoms are of comparative mildness in the patient, his brother, two sisters, his daughter and a nephew. The inheritance of the disease in a progressively milder form suggests eventual extinction of the disease in this family. Eleven members of the family are known to have been affected in six generations, with a mortality of 5.5 per cent, due to bleeding.

CASE 6.—Miss N. H., aged 16, was first seen during January 1944. She is the daughter of Mr. W. H., of case 5.

Mild epistaxis and telangiectases were first noticed in her at the age of 3. The symptoms became only slightly more severe as she grew older and have never been very severe.

A few pinpoint angiomas were found on the left side of the nasal septum and two larger ones on the right side. Widely scattered small lesions were present on the tongue, the lips, the neck, the arms and the fingers. One spider nevus was found on the palpebral conjunctiva.

Her more remote ancestors suffered from the disease in a very severe form. In her generation the symptoms and the angiomas are barely discernible, and no medical care is required.

CASE 7.—Mr. A. D., aged 17, was first seen on Jan. 12, 1944. He was a nephew of the patient in case 5 and a cousin of the patient in case 6. His father had suffered from the disease in a very severe form, and his facial telangiectases were so large and numerous that they constituted a definitely embarrassing disfigurement. On several occasions epistaxis had threatened the father's life.

The patient's first attack of epistaxis occurred very early in life; his approximate age at the time is not known. Angiomas appeared on his lips at 15 and continued to enlarge throughout his sixteenth year. Epistaxis has always been mild, and all the angiomas except those on the lips are small. Associated with the lesions are numerous freckles and pigmented nevi. The telangiectases were found on the nasal septum, the inferior turbinates, the lips, the face and the chest. His disease had not been diagnosed previously in spite of his history. On several occasions he had called the attention of his attending physician to his lesions and family history.

Both he and his cousin (case 6) belong to the sixth generation of their family to be affected by this disease. It is possible that the disease is becoming extinct in this family. It has become progressively milder, and Osler's disease has rarely been reported as affecting even as many as six generations.

SUMMARY AND CONCLUSIONS

The author presents a review of the literature from 1933 to 1944 and adds 7 cases which have never been reported previously.

The recent literature contains many valuable contributions concerning the possible genesis of the disease, the effects of heredity and the new methods of treatment. It is highly probable that in about 20 per cent of the recorded cases the disease developed in the total absence of a family history of its occurrence. Whether the patients in these cases can transmit the disease to their progeny is not known. The author adds

to the literature the third recorded instance in the last eleven years in which the disease can be traced through six generations in one family. The extreme rarity of this together with the fact that the disease has become progressively milder during the last two generations in this family suggests self limitation of the hereditary transmission of the disease. In the affected members of the two newly recorded families the symptoms and the lesions developed many years earlier than the ages usually reported.

The disease is generally regarded as simple ectasia of preexisting vascular channels, but it is not improbable that the lesions are actually multiple acquired neoplastic angiomas arising from endothelial rests of embryonal origin. This is suggested by the following observations: Epistaxis usually predates the development of visible mucosal or cutaneous lesions; satellite lesions develop in the region adjoining the site formerly occupied by angiomas destroyed by treatment; the lesions have a universal distribution and some are of great size; they have a tendency to disappear spontaneously while new angiomas appear; the microscopic and biomicroscopic pictures suggest neoplastic development; there is a slow and incomplete but definite response to roentgen therapy.

The newer methods of treatment include electrolysis, roentgen ray or radium irradiation, microinjection of sclerosing solutions and parenteral administration of moccasin venom. I observed good results in the single patient who was treated with roentgen rays by the "intermediate" method.

The literature includes many references to a possible relationship between Osler's disease and other diseases due not only to possible mesenchymal but also to possibly associated ectodermal dysplasia. These postulates are interesting but no final proof of any such relationship exists at present.

The 7 cases reported in this article were gathered during the past two and a half years in my own otolaryngologic practice. These cases had not been diagnosed previously. It is quite certain that a more widely disseminated knowledge of the disease will result in its more frequent recognition and diagnosis. Too little attention has usually been given to Osler's disease in undergraduate medical education.

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VITAMIN C–SULFONAMIDE COMPOUNDS IN THE HEALING OF WOUNDS

THE USE OF SULFANILAMIDE ASCORBATE IN THE TREATMENT OF CHRONIC SUPPURATION OF THE WOUND AFTER RADICAL MASTOIDECTOMY

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When von Jeney and Törö [1] added ascorbic acid to the nutrient medium of a culture of fibroblasts in vitro and observed a marked increase in the number of collagen fibrils, the basis was laid for an advance in the local treatment of wounds. Since the repair and the tensile strength of wounds in soft tissues are direct functions of the proliferation of fibroblasts and the formation of collagen, it is evident that vitamin C plays an important role in the phenomenon of wound healing. Saitta [2] reported delayed healing of exposed surface wounds in guinea pigs that had been kept on a vitamin C–deficient diet for more than fifteen days. On the other hand, when a vitamin C–containing extract was applied directly to the wound, the time of healing was appreciably diminished, regardless of whether the animals were maintained on a normal or a scorbutic dietary regimen. He determined the rate of healing by daily measurements of the length and the breadth of the wound.

In the handling of war wounds, time saved by quicker healing may be translated into savings not only of manpower but also of hospital beds and equipment.

In recognizing the influence of vitamin C in the healing of wounds several questions present themselves. Would an increase in the oral use of vitamin C accomplish the necessary result? What are the properties of ascorbic acid when applied locally to wounds and what concentrations are effective? The work of Lauber [3] throws considerable light on these questions. He excised measured square blocks of skin and subcutaneous tissue in experimental animals and noted the time required for complete healing and epithelization of the wounds. He found no acceleration in the healing of such wounds in guinea pigs which received subcutaneous injections of either small or large doses of ascorbic acid. The time of healing of similar defects of skin in mice 3 months old was reduced by three days when strong concentrations of cevitamic acid were applied to the surface of the wounds.

This corresponds to the observations of Bundesen and co-workers [4] in their studies on the cutaneous reactions of patients hypersensitive to arsenic. When ascorbic acid was applied locally to the area tested with an arsenical compound, the reaction was strikingly reduced. Ascorbic acid given by mouth did not influence the local reaction to any noticeable degree. The local effect of vitamin C has, therefore, a therapeutic role quite independent of the systemic action. On the other hand, a systemic deficiency of vitamin C producing a scorbutic or a prescorbutic state definitely affects wound healing. Thus, Lanman and Ingalls [5] observed imperfect healing of operative incisions in guinea pigs maintained on a low intake of ascorbic acid. In such animals the tensile strength of wounds of the stomach and the abdominal wall, measured ten, twenty and thirty days postoperatively, was greatly inferior to that observed in normal control animals.

Taffel and Harvey [6] made interesting observations in a series of well controlled experiments to determine the effect of absolute and partial vitamin C deficiency in the healing of gastric wounds during the first fourteen days after operation. In the animal showing absolute scurvy, they calculated a mathematically significant increase in the strength of the wound over that of the control animal on the fourth postoperative day. The significance of this increase is not evident, and they have suggested that in some way the absolute deficiency may act as a

1. von Jeney, A., and Törö, I.: The Effect of Ascorbic Acid on the Formation of Fibers in Fibroblast Cultures, Virchows Arch. f. path. Anat. **298**:87, 1936.

2. Saitta, S.: Scritti biol. **4**:301, 1929.

3. Lauber, H. J.: Vitamins and Healing of Wounds and Burns, Beitr. z. klin. Chir. **158**:293, 1933.

4. Bundesen, H. N., and others: The Detoxifying Action of Vitamin C (Ascorbic Acid) in Arsenical Therapy, J. A. M. A. **117**:1692 (Nov. 15) 1941.

5. Lanman, T. H., and Ingalls, T. H.: Vitamin C Deficiency and Wound Healing, Ann. Surg. **105**:616, 1937.

6. Taffel, M., and Harvey, S. C.: The Effect of Absolute and Partial Vitamin C Deficiency on Healing of Wounds, Proc. Soc. Exper. Biol. & Med. **38**:518, 1938.

stimulus for the increased proliferation of fibroblasts in the very early stages of healing. However, at the six day interval the strength of the wound in the scorbutic guinea pig was markedly inferior to that in the normal animal. This can be fairly attributed to the inadequate formation of collagen known to occur in vitamin C deficiency.

In the partially scorbutic guinea pigs on the fourth to sixth day there were no appreciable deviations from the normal. During the eight to ten day interval, however, there was a significant diminution in the tensile strength, which during the twelve to fourteen day interval again approached the normal value. This relative weakness in the wounds of the experimental group was further emphasized by a comparison of the sites of the bursting point, which in the partially scorbutic animals was at the operative area. The inferior strength of the wounds during the eight to ten day interval coincides strongly with the clinical experience that the majority of wound disruptions occur during this same postoperative period. These experiments demonstrate again that vitamin C deficiency in man, even when it is partial, may indeed be one of the major causative factors in those cases of wound disruption in which there is no evidence of infection of the wound and the patient for one reason or another has been on an inadequate dietary regimen.

The biochemical rationale for the local and systemic effects of ascorbic acid in wound healing reaches back to the work of Aschoff and Koch [7] in 1919, who suggested that in scurvy the primary deficiency consisted of a lack or a faulty development of intercellular cement substance. They surmised that the condition of the costochondral junction in human scorbutic material was due to the inability of osteoblasts to form osteoid tissue.

Wolbach and Howe,[8] studying the effect of the scorbutic state on the production and maintenance of intercellular substances, showed that the repair of soft tissues is likewise seriously affected. Proliferation of fibroblasts is apparently but little affected by the scorbutic state, but there is marked diminution in the amount of intercellular substance formed. Another striking effect is seen in the retardation of the formation of new blood vessels in the organization of lesions. They suggested that in the formation of intercellular substances there is a change of the material from a liquid to a solid or jell state and that the missing factor in the scorbutic condition is one affecting the jelling or setting of the liquid product. In absolute scurvy all deposition of collagen and other intercellular material ceases. If the scurvy is interrupted by supplying the experimental animals with adequate amounts of ascorbic acid, deposition of collagen promptly resumes.

Hass and McDonald [9] tried to define collagen but concluded that a satisfactory definition has never been devised. Morphologists regard collagen as a homogeneous or fibrillary intercellular protein which serves as the principal organic matrix of white fibrous connective tissue, bone and cartilage. They distinguish collagen from other intercellular materials by staining reactions, microscopic structure and other more or less empiric properties.

Chemists regard collagen as a protein which yields gelatin on partial hydrolysis. The source of collagen is unknown. In the processes of growth and repair it appears in the intercellular medium only in the presence of fibroblasts and is initially recognized as a specific entity in the immediate vicinity of these cells. It is thus generally believed that fibroblasts perform an indispensable role in the formation of collagen. Menkin, Wolbach and Menkin [10] by extensive experimental work arrived at the conclusion that "a relatively simple chemical substance, ascorbic acid, controls the deposition of intercellular substance." The possible mechanism involved in this reaction is discussed from the standpoint of the properties of ascorbic acid as a reducing agent in relation to cellular oxidation.

Recognizing the systemic effects of ascorbic acid and the absolute need of it in all tissues, the local employment of this vitamin in large doses is all the more intriguing. The possibility of increasing local tissue responses by increasing the concentrations of ascorbic acid has attracted the attention of many investigators, not only from the angle of the prevalence of the prescorbutic or mildly scorbutic state but also from that of the local action in allergic persons. This is particularly striking in Bundesen's report, which showed that the cutaneous reactions of patients who were hypersensitive to arsenic even when kept on an adequate ration of ascorbic acid

7. Aschoff, L., and Koch, W.: Skorbut: Eine pathologisch anatomische Studie, Jena, Gustav Fisher, 1919, pp. 56-84.

8. Wolbach, S. B., and Howe, P. R.: Intercellular Substances in Experimental Scorbutus, Arch. Path. **1:** 1-24 (Jan.) 1926.

9. Hass, G., and McDonald, F.: Studies of Collagen: The Production of Collagen in Vitro Under Variable Experimental Conditions, Am. J. Path. **16:** 525, 1930.

10. Menkin, V.; Wolbach, S. B., and Menkin, M. F.: Formation of Intercellular Substance by the Administration of Ascorbic Acid (Vitamin C) in Experimental Scorbutus, Am. J. Path. **10:**569, 1934.

were diminished by the local application of ascorbic acid simultaneously with the arsenical patch test. Thus the local effect of ascorbic acid is something independent of the systemic level of vitamin C.

The clinical importance of the systemic level of vitamin C in surgical patients was extensively studied by Holman,[11] who adopted the practice of administering ascorbic acid for two weeks prior to operation. Not only did he note that ascorbic acid requirements in surgical as well as in nonsurgical patients were considerably above normal, but in a study of the vitamin C content of the blood of patients admitted to the surgical clinic wards of Lane Stanford Hospital in San Francisco he observed that a surprising number of patients showed a low concentration of vitamin C in the blood. This was all the more remarkable in view of the cheapness and ready availability of citrus fruit in this region.

As a basis of his determinations, Holman used the urinary excretion and the blood concentration of ascorbic acid in infantile scurvy. He followed the Ingalls [12] levels (table 1). On this basis his

TABLE 1.—*Levels of Ascorbic Acid in the Plasma in Various States of Vitamin C Nutrition (After Ingalls [12])*

State of Vitamin C Nutrition	Plasma Ascorbic Acid, Mg. per 100 Cc. of Blood
Optimum	
Saturation	2.00 to 1.00
Normal	1.00 to 0.70
Low normal	0.70 to 0.50
Suboptimum	0.50 to 0.30
Deficiency	
Asymptomatic scurvy	0.30 to 0.15
Clinical scurvy	0.15 to 0.00

results showed that approximately 44 per cent of free clinic patients, who usually fall in the low economic group, gave evidence of being on a diet poor in vitamin C and that 9 of 70 patients were on the borderline of scurvy. Youmans [13] in a study of 16 presumably normal subjects found 8 to have evidence of vitamin C deficiency. Of 34 patients admitted to a London hospital, 14 showed evidence of vitamin C deficiency, and most of the remainder excreted not more than the minimum standard. All those above 70 years of age showed relative deficiency.

He was particularly impressed with the work of Taffel and Harvey,[6] who studied the healing of wounds in guinea pigs partially depleted of their vitamin C reserves and subsequently maintained at a low level of ascorbic acid supply. They considered the nutritional state of these animals to be analogous to asymptomatic scurvy and therefore probably analogous to the condition of 13 per cent of the clinic patients. Healing wounds in these partially scorbutic animals showed inferior tensile strength, a disposition to gape before rupturing, a livid appearance and a soft consistency of the granulation tissue. As a result, the abdominal wounds of this scorbutic group ruptured at a pressure averaging about one third of that required to rupture the wounds of normal animals.

In line with these observations is the clinical evidence of Archer and Graham,[14] who found the cause of death to be peritonitis in 16 of 51 patients who died after operations on the stomach at St. Bartholomew Hospital in London, England. In 12 of these the peritoneal infections appeared to have arisen as a result of bacterial leakage at the sites of anastomosis, where there was an almost complete absence of fibrous tissue response along the suture line.

The evidence of striking need of vitamin C in disease was shown for tuberculosis by Abbasy, Harris and Ellman,[15] for pneumonia by Harde, Rothstein and Ratish [16] and for osteomyelitis by Abassy, Harris and Hill.[17] It is little wonder that with these reports Holman [11] concluded that routine administration of vitamin C was indicated for all his patients. Holman's stand was well supported by Lund,[18] who studied the effect of surgical operations on the level of ascorbic acid in the blood plasma. Determinations of plasma ascorbic acid were made for 43 patients before and after major operations. In nearly every patient there was a prompt fall from the original level after operation. In a few the level began to rise again after four or five days.

Lauber and Rosenfeld [19] in histologic studies of the amount of vitamin C in the bodies of

11. Holman, E.: Vitamin and Protein Factors in Preoperative and Postoperative Care of the Surgical Patient, Surg., Gynec. & Obst. **70**:261, 1940.

12. Ingalls, T. H., and Warren, H. A.: Asymptomatic Scurvy, New England J. Med. **217**:443, 1937.

13. Youmans, J. B.; Corlette, M. B.; Akeroyd, J. H., and Frank, H.: Studies of Vitamin C Excretion and Saturation, Am. J. M. Sc. **191**:319, 1936.

14. Archer, H. E., and Graham, G.: On the Excretion of Ascorbic Acid, Lancet **1**:710, 1936; Subscurvy State in Relation to Gastric and Duodenal Ulcer, ibid. **20**:364, 1936.

15. Abbasy, M. A.; Harris, L. J., and Ellman, P.: Excretion of Vitamin C in Pulmonary Tuberculosis and in Rheumatoid Arthritis, Lancet **2**:181, 1937.

16. Harde, E.; Rothstein, I. A., and Ratish, H. D.: Urinary Excretion of Vitamin C in Pneumonia, Proc. Soc. Exper. Biol. & Med. **32**:1088, 1935.

17. Abbasy, M. A.; Harris, L. J., and Hill, N.: Excretion of Vitamin C in Osteomyelitis, Lancet **2**: 177, 1937.

18. Lund, C. C.: The Effect of Surgical Operations on the Level of Cevitamic Acid in the Blood Plasma, New England J. Med. **221**:123, 1939.

19. Lauber, H. J., and Rosenfeld, W.: Histologische Untersuchungen über das Verhalten des Vitamins C in den verschiedenen Organen während der Wundheilung, Klin. Wchnschr. **17**:1587, 1938.

guinea pigs on low vitamin diets found that when healing of wounds was in progress there were decreased amounts of the vitamin in the various tissues, suggesting that it had been utilized in the healing process. The vitamin C locally applied to wound tissue thus presents an additional factor in healing.

Another matter worthy of consideration is the relationship of ascorbic acid to the bacteria in the wound area. Kligler and Guggenheim [20] attempted to analyze the various factors in relation to the growth of Clostridium welchii and Clostridium tetani. They concluded that ascorbic acid served as a detoxicating agent both during and after the growth of the organisms. The relative rates of destruction of vitamin C in cultures of various organisms have been widely studied. Bacillus coli has been shown to be particularly active in this regard.

King,[21] in a number of papers, supported the view that vitamin C is of major importance in the detoxification process. He showed that injections of toxins or toxic materials may lead to marked depletion of vitamin C in the tissues and that animals whose tissues are moderately or severely depleted of their vitamin C reserves are subject to greater injury from injected toxins. Many observed that infants who were receiving a limited supply of the vitamin showed no sign of scurvy normally, but when they were subjected to the added stress of minor infections, indications of clinical scurvy appeared. Later, when the effect of the infection had passed, the signs of scurvy disappeared spontaneously. Kaiser and Slavin [22] observed a significant correlation between low values for the ascorbic acid in the blood and severe infections with hemolytic streptococci. Ruskin [23] showed that grippal infections cause rapid depletion of plasma ascorbic acid and that the otitic complication myringitis bullosa hemorrhagica, commonly called grip otitis, is actually a manifestation of acute scurvy with hemorrhagic vesicles on the external canal and the drum membrane. Incision of the drum membrane in such cases was usually followed by severe otitis and mastoiditis, at times complicated further by sinus thrombosis and intracranial disease. The organism usually was the hemolytic streptococcus. Ruskin observed rapid improvement in the original myringitis bullosa following administration of large doses of vitamin C. In all cases in his series the pathologic process came to rapid resolution. The combined use of ascorbic acid and sulfanilamide was effective in cases in which the disease was advanced.

The relationship of ascorbic acid to calcium and the healing of bone was first described by Ruskin [24] in a series of comparative studies of the action of calcium and vitamin C and, later on, in a chemical and physical comparison of vitamin C, calcium ascorbate and calcium gluconate. Bourne,[25] working at Oxford University, in England, confirmed this original work by a series of ingenious experiments. He bored cylinders of bone out of the femurs of groups of rats given vitamin C, calcium ascorbate and calcium gluconate, respectively. He observed that the animals receiving calcium ascorbate showed a mathematical increase of bone healing while those receiving vitamin C alone or calcium gluconate did not do better than the controls.

Further chemical study of the relationship of ascorbic acid to toxins led Sigal and King [26] to the conclusion that "in all cases (diphtheria toxin, virus, phenol) the effect was shown by a real chemical combination between vitamin C and the poisons." The chemical interaction between ascorbic acid and the sulfonamide compounds was taken advantage of in determining the amount of ascorbic acid in tissues. With the diazotized sulfonamide compound, Scudi and Ratish [27] were able to secure a quantitative color reaction even in the presence of cysteine and in citrus juices.

Ruskin and Jonnard,[28] in a study of ascorbic acid, showed by interferential refractometry that ascorbic acid has a pronounced tendency to form serum protein complexes. This may explain many of the valuable detoxifying properties of ascorbic acid.

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20. Kligler, I. J., and Guggenheim, K.: Influence of Vitamin C on Growth of Anaerobes in Presence of Air, with Special Reference to Relative Significance of Eh and O_2 in Growth of Anaerobes, J. Bact. **35**:141, 1938.

21. King, C. G.: Vitamin C, Ascorbic Acid, Physiol. Rev. **16**:238, 1936.

22. Kaiser, A. D., and Slavin, B.: Incidence of Hemolytic Streptococci in Tonsils of Children as Related to Vitamin C Content of Tonsils and Blood, J. Pediat. **13**:322, 1938.

23. Ruskin, S. L.: The Influence of Vitamin C on Wassermann Fastness in Syphilis, Am. J. Digest. Dis. **10**:170, 1943.

24. Ruskin, S. L.: Studies on the Parallel Action of Vitamin C and Calcium, Am. J. Digest. Dis. **5**:408, 1938.

25. Bourne, G.: The Effect of Ascorbic Acid (Vitamin C), Calcium Ascorbate, and Calcium Gluconate on the Regeneration of Bone in Rats, Quart. J. Exper. Physiol. **31**:319, 1942.

26. Sigal and King, cited by King.[21]

27. Scudi, J. V., and Ratish, H. D.: A Colorimetric Method for Determination of Ascorbic Acid, Indust. & Engin. Chem. (Anal. Ed.) **10**:420, 1938.

28. Ruskin, S. L., and Jonnard, R.: Studies in Calcium Metabolism: II. Further Contributions to the Comparative Studies of the Physicochemical Properties of the Gluconate and Cevitamate of Calcium and of Vitamin C, Am. J. Digest. Dis. **5**:676, 1938.

One of the physicochemical properties of ascorbic acid not yet fully appreciated is the one by virtue of which this substance combined with any of many poorly soluble substances becomes hygroscopic. This is true of procaine, ephedrine, strychnine, atropine and most of the alkaloids. It is this property which keeps sulfanilamide ascorbate and sufathiazole ascorbate spongy, thus preventing caking in wounds.

The histologic appearance of wounds in vitamin C deficiency was brilliantly described by Hartzell and Stone [29] in their study of the relationship of the concentration of ascorbic acid of the blood to the tensile strength of wounds in animals. For the determination of the strength of a wound the entire belly wall was removed and all the sutures were cut. Strips 1 cm. in width were cut perpendicular to the incision by means of a sharp razor blade. The tensiometer was used to measure the grams per centimeter of length of wound as read directly from the tensiometer scale. Four or five such strips were obtained for each animal and the average calculated. Thus, the average strength over the whole length of the wound may be estimated. In this respect their method differed from that used by others, who measured the pressure required to burst the wound open, thereby obtaining the strength at the weakest point. For the histologic study a 5 mm. strip was taken near the center of the wound.

The observations showed a striking difference in the appearance of the wounds in guinea pigs kept on a diet rich in vitamin C as compared with those in guinea pigs fed on a diet deficient in vitamin C.

In the normal guinea pigs, healing progressed rapidly. The wounds were clean, there was no oozing of blood from the margins or about the sutures, and there was no edema about the wound. On section there was no thickening of the belly wall and no evidence of hemorrhage into the wound. The wounds in almost all these animals appeared well healed by the sixth to the eighth postoperative day, and by the tenth to the fourteenth postoperative day the incision was white and smooth.

In guinea pigs fed diets deficient in vitamin C the wounds presented a very different appearance. Almost without exception there was edema along the suture lines with some redness. Heavy bloody crusts formed soon after operation and were almost invariably present on the eighth to the tenth postoperative day. Although appearing well healed on the fourteenth day, the incision was still hard and raised, with some crusts still present. When the belly wall was sectioned, it was found to be thickened and often presented a hemorrhagic appearance.

Microscopic sections of wounds in control guinea pigs and animals partially deficient in vitamin C showed marked differences as early as the fourth postoperative day. In the control animals the epithelial bridges were complete, though the thickness of the epithelium varied with different guinea pigs. A slight exudation of serum, red blood cells and neutrophils was found in the corium and between muscle bundles. A moderate fibroblastic proliferation was evident in the deep portion of the corium, but only a few thin collagenous fibers could be seen. Numerous foreign body giant cells and focal collections of mononuclears were detected at the edges of the wounds.

The slides of the partially deficient group showed at the fourth day well healed epithelium. The reticular portion of the corium and the subcutis showed numerous pools of serum containing red blood cells and a few lymphocytes. Fibroblastic proliferation was more marked than in the control animals, but production of collagen was scant. The presence of a hemorrhagic effusion was constant in all deficient animals.

At the sixth day the wounds of control animals showed an increase in fibroblastic proliferation, the production of mature collagen, especially in the corium, as well as in the muscle layers. The wounds of the corresponding deficient guinea pigs presented marked exudation of fluid containing red blood cells. The exudate was seen throughout the entire extent of the wound but was most marked in the reticular layer of the corium and in the subcutis. Proliferation cells were as numerous in deficient animals as in controls, but the production of collagen was definitely retarded. This difference was even more pronounced in the eight day comparison. The wounds in almost all deficient animals showed small pools of serum and red blood cells separating the wound edges. These pools were usually present in the deep layers of the corium but could be found throughout the entire wound.

By the fourteenth day the wounds of the control animals were almost completely healed. The collagen was dense, and the fibrocytes were apparently mature. In the muscle layers a large amount of collagen was present with only mild cellular proliferation. As to deficient animals at fourteen days, good wound repair was seen in some, but in many the wounds gaped at various levels. Little effusion could be seen, but marked

29. Hartzell, J. B., and Stone, W. E.: The Relationship of the Concentration of Ascorbic Acid of the Blood to the Tensile Strength of Wounds in Animals, Surg., Gynec. & Obst. **75**:1, 1942.

cellular proliferation was present in most instances. The amount of collagen varied with each animal. The maximum production was usually found in the corium.

In animals deficient prior to operation but given ascorbic acid daily after operation, healing was delayed during the first six days. Small effusions were observed in some animals, and production of collagen was delayed in all. By the eighth day after operation, however, the wounds appeared almost as completely healed as those in the control group.

The tensile strength of the abdominal wounds also showed a mathematical difference. The four day wound of a normal guinea pig had a tensile strength of 183 Gm. per centimeter of wound while that of the animal deficient in vitamin C gave a value of 38 Gm. The value for the six day wound of the normal guinea pig was 674 Gm., and the corresponding wound of the deficient guinea pig had a tensile strength of 291 Gm. The eight day wound of the normal animal had a tensile strength of 1,127 Gm. per centimeter while that of the deficient animal had a strength of 345 Gm. per centimeter. These figures thus establish an experimental mathematical basis for uniform ascorbic acid therapy.

This work could also be viewed as a further confirmation of the work of Hunt[30] at St. Bartholomew Hospital in London. Hunt further showed the importance of vitamin C in phagocytosis in wounds and in the absorption of damaged tissues and the removal of the catgut used in ligatures—all elements in rapid and effective healing. The oxidation-reduction properties of ascorbic acid are undoubtedly important in these functions. He stated that wound disruptions have been reduced by about 75 per cent since the routine administration of ascorbic acid was adopted for all major abdominal operations, thus confirming the experimental results clinically. By analogy with the experimental clean healing of wounds, it is reasonable to presume that all subacute and chronic infective lesions would be assisted in their healing by saturation of the patient with vitamin C. Hunt categorically stated that it should be administered (1) when clean and quick healing of the wound is particularly desirable, (2) in major abdominal operations, (3) when a hollow viscus has been opened, (4) when postoperative complications are anticipated, (5) when there is evidence of nutritional deficiency and (6) in all cases of serious injury. He concluded that vitamin C in good concentration is of the greatest importance in the healing of wounds.

30. Hunt, A. H.: The Role of Vitamin C in Wound Healing, Brit. J. Surg. **28**:436, 1941.

Simultaneously he called attention to the wide use of sulfanilamide powder following the bombing of London, where physicians had an opportunity to test the efficacy and observe the effects of the sulfonamide compounds in potentially infected wounds. He concluded that "the powder sprinkled into the excised wound indubitably delays healing." The experimental work of Bricker and Graham further confirmed Hunt's observations.

The possibility of using vitamin C in chemical combination with the sulfonamide drugs opened up a most interesting avenue of investigation. This was particularly so since the chemical properties of ascorbic acid were such as to reduce the alkalinity of the sulfonamide drugs. The vitamin also lends a hygroscopic factor which tends to prevent caking of sulfanilamide, thus prolonging uniform absorption. The tendency of vitamin C to form serum protein complexes, as shown by Ruskin and Jonnard,[24] serves to increase absorption and utilization of sulfonamide compounds. This serum protein–combining property of ascorbic acid is probably responsible for the detoxifying effect of vitamin C on sulfonamide compounds. Martin,[31] of the Warner Research Institute, in April 1943, at a meeting of the American Chemical Society in Buffalo, declared that vitamin C should be fed in especially large amounts to all persons under treatment with sulfonamide drugs. This amount is accurately obtained in the molecular compound of sulfanilamide ascorbate or sulfathiazole ascorbate.

In order to have visual control of the advantages of the sulfonamide ascorbate, it was deemed expedient to use the sulfanilamide ascorbate in chronic, nonhealing wounds of long standing where bone would particularly be involved. This was especially to be desired in view of the work of Bourne on defective healing of bone in vitamin C deficiency. Such easily visualized wounds involving bone are found in unhealed cavities following radical mastoidectomies and in ears with chronic suppurative otitis media and defects of the drum membrane. The routine of the procedure was to irrigate the ear cavity, dry the area and then fill the mastoid cavity, the middle ear and the external canal with the sulfanilamide ascorbate.[32] Pre-

31. Martin, S.: Personal communication to the author.

32. Sulfanilamide ascorbate and sulfathiazole ascorbate represent a conjugated form in which sulfanilamide is combined equimolecularly with ascorbic acid. The compound is stable in the powder form, in which it is used, and a solution containing it in a concentration of approximately 1.5 per cent is stable. The procedure, which is described as frosting, is the application

vious trial of plain sulfanilamide proved it to be irritating and productive of a fairly profuse serous discharge and so its use had to be discontinued. This was not the case with the sulfanilamide ascorbate, which was well tolerated and formed a moist filling of a golden yellow color.

The sulfanilamide ascorbate pack was allowed to remain in situ for one week. Virtually with the first application the characteristic foul odor disappeared. At the end of the first week the sulfanilamide ascorbate was swabbed out and a fresh filling of the wound, middle ear and canal was made.

One group of the cases here recorded was particularly interesting since it represented the postoperative radical mastoid wound that had failed to respond to years of customary treatment.

REPORT OF CASES

Case 1.—Marie V., aged 38 years, in June 1940 had undergone left radical mastoidectomy at the Medical Center, in New York. On May 1, 1942 the wound continued to show a profuse foul discharge from the antrum-attic region. Granulations filled the attic-antrum area and partially occluded the external canal. The wound was washed and dried, and then the mastoid cavity, the middle ear and the canal were filled with sulfanilamide ascorbate. The powder was allowed to remain for one week, during which time it was partially absorbed. Virtually with the first application the odor disappeared and the discharge diminished. Epithelization of the mastoid cavity proceeded rapidly, and after the fourth weekly filling the wound was dry, healed and epithelized. This was on July 5. She has not required any further care for her ear.

Case 2.—Vincent D., aged 40, who underwent a radical operation on the mastoid process in 1923, had continued suppuration for the ensuing twenty years despite a wide variety of treatments from several otologists, including myself. Almost all of the wound cavity was epithelized; the excepted area was in the antrum-attic region, which discharged every few days. Usually, prior to the discharging the patient had an attack of "spots before the eyes," which was relieved partially after the ear was cleansed. Irrigation of the ear with a solution containing sodium sulfathiazole was usually followed by a profuse serous discharge during the following twenty-four to forty-eight hours; this seemed to be an allergic reaction. On March 31, 1943 treatment with sulfanilamide ascorbate was started. The sulfanilamide ascorbate pack produced a striking difference in the healing response of the cavity. For the first time one could observe fresh epithelization in the attic-antrum region. There was no evidence of irritation. The patient complained of some discomfort from the packing of the external canal with the sulfanilamide ascorbate, so that in subsequent treatments frosting by insufflation of the powder was employed. After the first few treatments the ear was greatly improved, and after the tenth application complete epithelization of the attic-antrum region was attained. The ear has remained dry and healed since April 30, 1943. On May 27 the patient reported that the "spots before his eyes" had disappeared and that coincidentally his sense of smell, which previously was poor, had returned. On September 25 he reported that his ear had continued completely dry even though he had had several colds.

Case 3.—Sidney S., aged 47, had had a discharging right ear for thirty-five years. In childhood he had undergone simple mastoidectomy and later radical mastoidectomy. He had associated left maxillary sinusitis with nasal polypi. The middle ear and mastoid cavity showed only slight epithelization with profuse purulent discharge. On May 13, 1943, the cavity and the middle ear were washed and dried; then, after the first packing, which remained for one week, frosting of the whole area with sulfanilamide ascorbate was performed. Epithelization proceeded rapidly, and after the eleventh treatment the cavity and the middle ear were sufficiently dry so that on July 18 the patient could be discharged from further care. The frostings were done twice weekly.

Case 4.—The patient was Herbert S., aged 25. Eighteen years before radical mastoidectomy had been performed on his left ear. For the same length of time he had had a chronic discharge from the right anterior attic region. The operative cavity was fairly well epithelized, but the middle ear showed granulations and erosion of the promontory. After the third sulfanilamide ascorbate pack the ear was virtually dry. The granulations disappeared, and an S-shaped erosion could now be seen on the promontory. Epithelization of the middle ear could be seen extending from the area of the mastoid antrum. Although there is still slight discharge, the area is epithelizing progressively. Sulfathiazole ascorbate, tried for several treatments, appears to be equally effective.

Case 5.—Bernard B., aged 52, underwent a radical operation on the mastoid process in 1908. Several weeks later he was operated on again because of extension of the infection. Following this, there was evidence of a fistula of the labyrinth, and there were recurrent attacks of vertigo. At times these attacks were so severe as to require hospitalization of the patient. He had been under intermittent care since 1927, but at no time was any tendency toward epithelization of the attic of the middle ear or antral cavity seen. The best that could be accomplished was the cleansing of the ear. Following three weeks of treatment with the sulfanilamide ascorbate pack, fresh epithelization was observed for the first time, associated with diminution of the discharge and disappearance of recurrent attic-antrum granulations. Because of the appearance of vertigo, from the pressure of the pack, frostings were subsequently employed.

Case 6.—Nathan Z., aged 27, gave a history of having undergone simple mastoidectomy two years before and of having continued to have a profuse foul-smelling discharge. Examination showed almost total absence of the drum membrane, with granulations filling the middle ear cavity and erosion of the attic-antrum region. Conservative treatment had been unavailing, and he had been advised to submit to radical mastoidectomy. On Aug. 20, 1942, after the ear had been cleansed and dried, sulfanilamide ascorbate packs were employed. Following the fifth pack the middle

of a light layer of the sulfanilamide ascorbate, which is blown into the wound cavity with a powder blower. This is contrasted with the packing in which the sulfanilamide ascorbate fills the entire cavity of the radical mastoid wound middle ear and canal.

ear and the antrum-attic region were dry and apparently healed. The patient was discharged on September 7.

CASE 7.—Shirley Z., aged 16, sister of the patient in case 6, gave a history of having undergone simple mastoidectomy on the left side one year before, with poor healing and continuing discharge from the middle ear and antral region. The otologist who performed the operation desired to reoperate on the mastoid area. In view of the improvement in her brother's case, she withheld consent for operation till the sulfanilamide ascorbate treatment could be tried. This was started June 17, 1942. Following the sixth pack, the middle ear was dry and healed on July 13, and the patient was kept under observation till September 30, during which time the ear remained dry. She was then discharged.

The next group comprised a series of 8 cases of chronic suppurative otitis media in which no operation had been performed but in which the defect of the drum membrane was almost total. The period of suppuration ranged in most instances back to early childhood.

These cases of otitis media were considered especially favorable for study because of the opportunity to note the influence of the sulfonamide ascorbate on bone healing as well as epithelization. In the ear this could be observed under direct vision. There was a boy, M., aged 12, who had a large unhealed retroauricular fistula; after repeated sulfanilamide ascorbate packs, the epithelization could be seen extending in finger-like prolongations toward the antrum. The patient had undergone several attempted closures and had refused further operative procedures. The size of the denuded area has diminished to less than half the initial size in a period of three months of weekly packs.

The use of sulfanilamide ascorbate and sulfathiazole ascorbate in post-tonsillectomy wounds was also observed. The clinical impression as to its use is most favorable. It is difficult, however, to draw mathematical conclusions since these wounds customarily heal well and comparative controls are not accurate except over a large series of cases. The sulfonamide ascorbate was used as a frosting in the course of the postoperative days.

The most interesting field of usefulness for the sulfonamide–vitamin C compound would apparently be in war wounds inasmuch as the vitamin C of the patients could be sufficiently low to be an important factor in wound healing. The use of sulfonamide ascorbate would automatically provide a sufficiently high local concentration to assure good healing. Another aspect of its use is in the routine oral administration of sulfonamide drugs, as the detoxifying properties of ascorbic acid have become collaterally available in an already chemically combined form.

TABLE 2.—*Summarization of Eight Cases of Chronic Suppurative Otitis Media with Almost Total Defect of the Drum Membrane*

Name	Age	History	Treatment *	Result
Faye J.	10	Otitis in course of scarlet fever four years ago, with nasal smear positive for diphtheria at that time (left ear)	Sulfanilamide ascorbate; three packings	Middle ear dry
Jack M.	35	Ear discharging since childhood; total defect of drum membrane with granulations; acute exacerbation following washing hair (left ear)	Sulfanilamide ascorbate; two packs	Middle ear dry
Tessie R.	27	Recurrent chronic otitis since 1936; on recurrence, 9/22/42, was advised to have radical mastoidectomy (right ear)	Sulfanilamide ascorbate; two frostings	Middle ear became dry and has remained healed
Mary B.	32	Intermittent discharge from middle ear since 1927; for last six months continuous discharge (left ear)	Sulfanilamide ascorbate; two frostings	Middle ear dry
Frank B.	21	Had large postscarlatinal defect of drum membrane, which was dry; recurrence of discharge one month ago (left ear)	Sulfanilamide ascorbate; three frostings; sulfathiazole ascorbate; final treatment	Middle ear dry
Freda N.	32	Recurrent right chronic suppurative otitis media for four years	Sulfathiazole ascorbate; one frosting	Middle ear dry
Florentine S.	24	For two months had had bloody discharge from right ear; has had recurrent suppuration of middle ear for several years; attic-antrum granuloma	Sulfanilamide ascorbate started 4/18/43	Middle ear dry; granuloma completely gone 4/28/43
Philips S.	36	Left ear discharging continuously for 15 years; chronic mastoiditis with attic-antrum discharge; foul odor	Sulfanilamide ascorbate pack; now sulfathiazole ascorbate frosting	Discharge from middle ear diminished; not foul; patient feels improved

* Prior to the sulfanilamide ascorbate pack or frosting, the ear was thoroughly irrigated, cleansed and dried with cotton swabs.

CONCLUSIONS

The role of vitamin C in wound healing is now firmly established, and its routine use in all surgical and traumatic cases is indicated. It should also be used in conjunction with other therapeutic agents in cases of infection.

Ascorbic acid stimulates the healing of wounds and counteracts the delay in healing incident to the use of sulfonamide compounds.

Sulfanilamide ascorbate and sulfathiazole ascorbate both show a definite capacity to heal chronic suppurative otitic infections and to stimulate healing with epithelization.

32 East Sixty-Seventh Street.

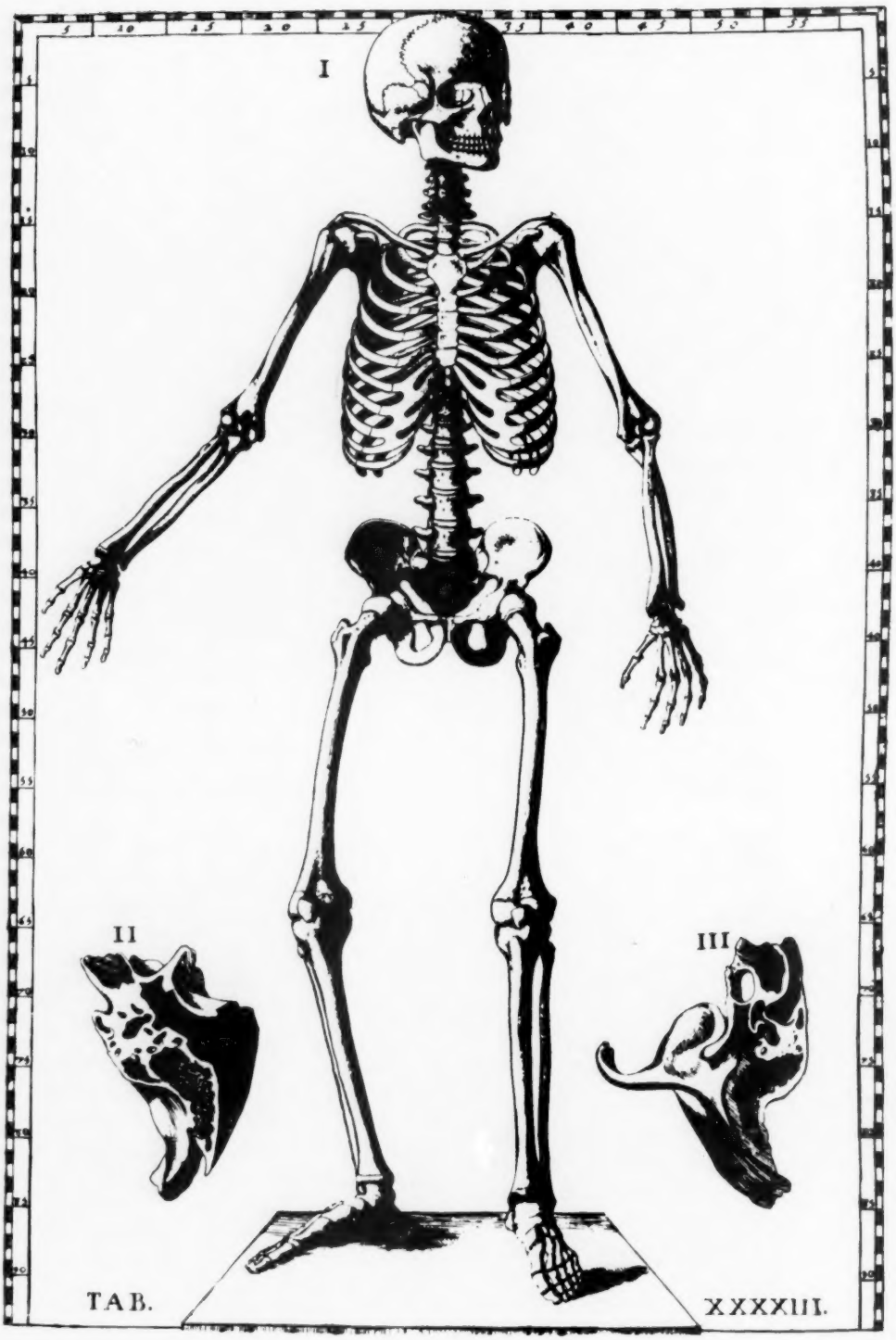

Fig. 1.—An illustration of the Epistle: *I*, skeleton, front view; *II*, temporal bone sawed through inner ear; *III*, inferior surface of temporal lobe.

EPISTLE ON THE ORGANS OF HEARING BY BARTHOLOMAEUS EUSTACHIUS

DEDICATED TO FRANCIS ALCIATUS, BISHOP OF MILAN DURING THE REIGN OF POPE PIUS IV

TRANSLATED BY

GRANT O. GRAVES, M.D., AND MAURICE E. GALANTE, B.A.

COLUMBUS, OHIO

Your distinguished high character and a singular desire of praising it compel me to bring to completion things that I think will please you greatly, and at the same time compel me to recount your merits profusely. . . . Your integrity, the principles of your life and the pleasantness of your habits are to me a rule and an end which all good men, moved by a feeling of emulation, should try to reach even though it really cannot be reached, but only neared. Very rarely does one find a person that can be matched with you, since you live with such great prudence and possess such ties that however much Fortune helps you, yet you do hold it in your control.

You are indeed in such a high and dignified position that even though you have been greatly helped by Fortune, yet much more it is due to your virtue, and I hope that you will yet arrive at that position of honor to which only a few, after many labors and long vigils, are able to come toward the end of their life when they are quite old. . . .

This fact plainly shows the liberality and nobility of your character: Even though you did not know me well, you thought me worthy of your patronage because of your great benevolence. And this has a much greater value to me because you will derive little advantage out of it, since I am an insignificant person.

By interpreting medicine in public, purposely disregarding the past, I presented to certain malignant men the opportunity of trying to alienate from me the good will of the Magnificent Cardinal Borromeo, and they would have succeeded easily if you had not frustrated their wishes. But it is still more admirable that you not only kept his good will toward me, but indeed you increased it greatly. . . .

But why so many words? If I gave my own life for your cause, I would still be greatly indebted to you. Therefore I think that under the auspices of the good God you thought that others were trying to render me damage, so that you bestowed great favors on me and in such a manner that I survived all disparagement and envy from other people. Indeed, whatever I have received and accepted I owe to your humanity and goodness, and to no merit of mine. . . .

Since then, I know that you, being well versed in almost every kind of study, and the most scholarly of men, had once desired to be convinced whether Galen dissected only apes and many other brutes, or men also, I easily guessed that you took delight in the faculty of anatomy, which deals with the knowledge of very beautiful things, emulating certain highly distinguished men, and especially Flavius Boethus and Sergius Paulus, the Roman Consuls, who within the memory of our ancestors took pleasure in investigating the wonderful industry of Nature in forming animals. On this account, and also because the abuse and calumnies with which the envious tried to pursue me you heard with your ears in such a way that they could do me no harm, I have collected a few facts worthy of knowledge but not as yet generally observed concerning the organs of hearing, making the subject of my writing that part of the body whereby you did me the greatest service. May I dedicate to you as a testimony of your benefits to me and of my gratitude to you this study of mine, trusting that the knowledge of things which have escaped the notice of others will be pleasing to you, and at the same time hoping that it will become customary for all students of anatomy to confess themselves greatly in your debt on this account as well? For, unless perhaps common *amour propre* deceives me, this letter, which comes into the light of day on your account, will instil into them a great longing and eagerness to contemplate the cleverness of Nature and her admirable craftsmanship in connection with things which,

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A translation of Eustachius, B.: Opuscula Anatomica: De auditus organis, ed. 2, Lugd. Bat., J. vander Linden, 1707, pp. 124-142.

Photostatic copies of the pages of the original work were furnished to us for translation through the Library of the Surgeon General's Office.

though they have been with all zeal and toil and diligence investigated and searched out, yet have not been found out and discovered, not even by those—otherwise most diligent and learned men—who have persuaded themselves that they have left to later anatomists no place for investigation, not to speak of discovery. But come, let us get to our subject.

The organs of hearing have been carelessly described by the philosophers and physicians who hold first place; for they hold that a nerve of the fifth pair of those which rise in the cerebrum proceeds through a certain twisting passage and ends in the membrane which is drawn across the opening of the ears; and they think that this membrane, since it is thin, dry and taut, when struck by air, with the help of the hardness of the bones which resemble a cave [antrum] or snail [cochlea], produce sound, without any other mechanism of Nature. Later [scholars], having investigated with greater zeal the art of this same Nature, claim to have found two small bones [ossicles] in a cavity of the stony bone [Lapideum Os], of which they have compared one very appropriately to a square anvil [incus] or a molar tooth, and the other to a hammer [malleus] or a femur, but in my opinion not aptly; for the end of the femur terminates in two processes, and its upper head and neck are small in proportion to its size, as Galen asserts and actual dissection shows; but the end of this ossicle is slender and sharp, while its head is so large that it may be regarded as the more important and thicker part of it. To be sure, Galen has nowhere, so far as I know, mentioned these bones, which are the smallest of all, and yet they are not, as some write, to be neglected because of their tininess, since their usefulness is not small, and their craftsmanship ["the Art"] proves the great wisdom of the Creator in shaping them; perhaps some one might say he described them in the book "On Obscure Movements," which we have lost through the ravages of time, or at least alluded to them in his little book "On Bones," where in the end he says he deliberately passed over certain ossicles; but the first conjecture is idle and little consonant with reason; the latter argument is not at all satisfactory, for, as he seems deserving of excuse if in an abbreviated book, in which class belongs the one entitled "On Bones," he does not explain everything, especially difficult things, exactly and minutely, just so he cannot avoid just censure for having made no mention of these ossicles in other long and detailed treatises. Besides, so far as I myself know, these two ossicles were first pointed out by Alexander Achillinus, the eminent philosopher of Bonn, and Jacob of Carpi, the surgeon and anatomist, who did not deserve so much contempt, although, when certain most ungrateful men subsequently stole [his discovery] so that it was counted of little moment by everybody, they did not blush to call him the most worthless of anatomists. Yet neither ever took it on himself to claim for himself the palm of discovery. Those who followed them wrote of the structure of the same bones just as if they themselves had discerned before any one else the industry of Nature in forming them, and yet the fair thing for them in judging others' writings would have been so to conduct themselves that men might not get the idea that they were criticizing mistakes with greater diligence and zeal than they were praising noble and useful discoveries. The third of these ossicles, which some call the staff or stapes, perforated in the middle, with a flat uneven surface, and having a triangular shape, became known later, and concerning its discovery many dispute today, while some, stricken by conscience, by no means dare to defraud the discoverer of his just praise; but they strive to persuade people that no physician, especially among those who live at Rome and profess anatomy, had known this bone at the time when they themselves were exhibiting it in public gymnasia, and they bestow the praise for the discovery on John Philip of Ingrasia, the outstanding Sicilian physician and philosopher. But let each man bestow that credit on whomever he prefers; I know at least that I, without being taught or advised by any one, was acquainted with this bone long before they wrote and that I showed it to not a few at Rome and had it carved in bronze; and it will now become clear from what I am about to explain, unless I am mistaken, whether I have investigated and discovered the organs of hearing by my own efforts or whether I have rather made use of others' work and claimed as mine what was rightly discovered by them, and now attempt to recount it to others.

The man who is regarded by almost everybody as the discoverer and, as it were, the architect of the anatomic art of today, asserts that the fifth pair of nerves of the cerebrum is carried through a very twisted opening especially made for it into a cavity prepared for the organ of hearing, and there splits in different directions and sends certain branches, broadened out like a membrane, to the base of this cavity, and even constitutes not the least part of the organ of hearing; he adds nothing further, thinking this all that has been discovered and found out about the organs of hearing. Now, if you will consider with me, with a fair mind, for the sake of finding out the truth, this and also many other things which he writes about this matter, I do not doubt that you

BARTHOLOMÆI EUSTACHII

EPISTOLA

DE

AUDITUS ORGANIS.

FRANCISCO ALCIATO
MEDIOLANENSI EPISCOPO
Civitatenſi, Sanctiſſ. Domini N. Pii IV.
Datario, Bartholomæus Euſtachius
Sanctoſeverinas Felicitatem.

EXimia Tua Virtus, ſingulariſque in me ornando voluntas, me hortantur atque adeo compellunt, ut enitar ea perficere, quæ cogitem Tibi fore gratiſſima; ſimul & in Tuis laudibus aliqua ex parte recenſendis (omnes enim oratione mea complecti non poſſem) oſtendere, mirum non eſſe, ſi omnes ad Tui amorem ita inflammentur & rapiantur, ut ſe Tibi multum debere ſentiant, me autem plurimum, & ſentiam, & prædicem: nam Tua integritas, vitæ inſtitutum, atque morum ſuavitas, tanquam regula quædam, & quaſi ſcopus mihi præfixus eſſe videtur, ad quem licet boni omnes, certa æmulatione moti, ſtudeant collimare, tamen vel nunquam, vel vix attingere poſſunt; quotus enim quiſque eſt, qui ſit

ſit Tecum conferendus? etenim magna prudentia ſingularique virtute præditus ita Te geris, ut quamvis Fortuna maxime adjuveris, tamen ſic eam arbitrio Tuo regis, ut ipſa Tibi parere cogatur, & nihil poſſe videatur: nam etſi in alto Dignitatis gradu collocatus es, multiſque Fortunæ præſidiis auctus, tamen Virtuti Tuæ multo plura, quam acceperit, debentur, & ſperamus fore, ut brevi ad eum honoris gradum pervenias, ad quem perpauci poſt multos labores, longaſque vigilias, extrema ſenectute pervenire potuerunt; ſiquidem eo conſilio, eaque moderatione vitam ducis, Teque altius provehi ſinis, ut quæ alios impediunt, quominus ad ſummum Dignitatis & Authoritatis apicem perveniant, Te remorari minime poſſint; nam admirabilis in Te Pietas Religioque elucet, & ſumma in rebus gerendis Prudentia, qua tum præſentia cognoſcis, præteritorum non oblitus, tum futura longe proſpicis: quamobrem quæ aliis difficilia ſunt, Tibi fiunt facilia & expedita; nemo Ingenium, Eloquentiam ac Doctrinam Tuam non admiratur, adeo temperantem te oſtendis, & optimis moribus præditum, ut omnia facile modereris, magnaque humanitate ſuavique conſuetudine omnes, qui Te norunt, allicias, utque Te ament, colant, & obſervent, pene compellas. Equidem dum hæc conſidero, non poſſum me continere, quin Te aſſidue laudem; ſed merita Tua multo majora ſunt, quam ut poſſint oratione mea pro dignitate ornari: dubitarem autem, ne viderer aſſentatiuncula quadam Tuam gratiam aucupari velle, niſi quæ a me dicuntur ita nota eſſent, ut concedi oporteat, invidos potius exiſtimandos eſſe eos, qui Te non admirantur, quam aſſentatores, qui hoc modo laudant. Illud vero Liberalitatem Altitudi-

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nemque animi Tui liquido patefacit, quod Tuo me patrocinio Tibi nondum cognitum, pro ſingulari humanitate Tua, dignum judicaſti, quod quidem beneficium eo majus videri debet, quo minor erat abs Te, propter tenuitatem meam, utilitas, aut præmium aliquod a me, quia nihil merebar, & tibi notus non eram, liberale aliquod officium exſpectandum. Ego ſane Medicinam publice interpretari juſtam ob cauſam ſuperioribus diebus intermittendo, occaſionem præbui malevolis quibuſdam hominibus, ut Borromei Cardinalis Ampliſſimi voluntatem a me alienarent, idque fuiſſent facillime conſecuti, ni (quæ Tua fuit humanitas) malevolorum animum ac deſiderium fruſtrari curaſſes; & quod admirabilius eſt, ſponte meque inſcio, tanti Principis in me voluntatem non modo conſervaſti, verum etiam mirum in modum auxiſti: quod quidem officium, & ſtudium erga me Tuum, tantum mihi oneris impoſuerunt, ut niſi Tua me Virtus munificaque natura ſuſtinuerit, cogar profecto ſuccumbere: quid verbis opus eſt? ego vel ſi vitam Tua cauſa profunderem, nullam partem Tuorum in me beneficiorum viderer conſecutus: equidem reor Dei Optimi Maximi conſilio injuriam mihi alios facere cogitaſſe, ut contra Tu tanto me beneficio ornares, ac ſimul provideres, ut Tuo patrocinio munitus, omnem jam detractionem atque invidiam ſuperarem; id vero totum ſummæ Tuæ humanitati ac bonitati acceptum refero, nulloque merito meo contigiſſe fateor: facio autem multo pluris propenſam hanc Tuam in me voluntatem, quam beneficia ipſa, quæ hactenus accepi, quæque ut ſperem etiam in poſterum, facit ſuavitas Ingenii Tui cum liberalitate conjuncta, & mirificum homines juvandi de-

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ſiderium: poſſem autem ingrati animi nomine jure condemnari, niſi operam darem, ut non ſolum prædicatione ac verbis, ſed re & opera conarer tanto beneficio aliqua ex parte ſatisfacere; ſed quando tenues vires meæ, & humilis ſtatus, diſparque ac multum jactata fortuna minime patiuntur, ut eo modo, quo cuperem, id exſequi poſſim, putavi mihi faciendum, ut pro mea facultate exſequerer, ea ſcilicet Tibi tribuendo, quæ a me tribui poſſunt maxima. Cum igitur intelligerem, Te in omni fere diſciplinarum genere verſatum, omniumque ſtudioſiſſimum deſideraſſe quandoque tibi demonſtrari, num Galenus ſimias, & pleraque alia bruta tantum, an homines quoque ſecuerit, facile conjeci Anatomica Te facultate, quæ circa pulcherrimarum rerum cognitionem verſatur, delectari, Ampliſſimos quoſdam Viros æmulatum, ac Flavium præſertim Boethum, & Sergium Paulum Conſules Romanos, qui Majorum memoria admirabilem Naturæ induſtriam animalibus conformandis cum voluptate perſcrutati ſunt. Cum ob eam rem, tum etiam quia Auribus maledicta & calumnias, quibus me invidi perſequi conabantur, ita audiviſti, ut nihil mihi, Te Patrono, obeſſe potuerint, collegi nonnulla ſcitu digna, neque hactenus percepta de Auditus Organis, eaque in hanc epiſtolam conjeci, ut ſumpto ab illa corporis parte, qua mihi maximam utilitatem attuliſti, ſcribendi argumento, hanc Incubrationem meam, quaſi teſtem Tuorum in me meritorum, & grati mei erga Te animi, Tibi dicarem, confidens jucundam Tibi fore eorum cognitionem, quæ alios latuerunt, & ſimul ſperans uſu venturum, ut hoc etiam nomine omnes Anatomiæ ſtudioſi tibi ſe plurimum debere fateantur; nam, niſi fortaſſe me communis

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Fig. 2.—Pages 125 to 128 of the Epistle.

will realize that they are far from the truth, and you will in the future hold suspect the structure described by him in many things; for, although no good man ought to be either a belittler of the common benefit which he has conferred on the art of medicine, or an enemy to virtue, or envious of praise, and although I have always thought that men's eminence deserved imitation, not envy, yet I believe the mistake of these same men, which can do harm, ought to be accurately pointed out and with all zeal avoided and shunned; since friendship should not be preferred before truth, nor persons favored rather than virtue; but both of these temptations should be especially shunned by those who wish to be considered honest and good men; and lest someone think me an abusive reviler, I should like to beg all students of anatomy first to read with attentive mind and scrutinize with open eyes what is written and pictured by that author in the eighth and twelfth chapters of his first book and the eighth chapter of the fourth book, then to compare the text and illustrations with what clearly appears in dissection, laying aside all emotions; for I am certain that when they have faithfully done this they will at once begin to reject what they accepted with the greatest admiration as true. Who, I ask, that is skilled in this art, would not censure this distribution of the fifth pair of nerves which arise in the cerebrum? This, to tell the truth, he invents arbitrarily and depicts as he chooses, along with the broken open temporal bone. Who, I beg, would allow him in the future to describe so loosely in words and drawings the cavities of the ears, constructed with marvelous skill?—since (I say this unwillingly, I call God to witness) neither in text nor picture is there any truth; indeed, he imagines three cavities, of which one most closely resembles a horn slightly twisted back twice, the second a snake moderately contracted in coils, and the last a straight walking stick; but there is nothing they represent less than the cavities and passages of the ears.

The later applauders and emulators of the authority and discoveries of this man, who are nurtured by new Athens, discoverer of all branches of knowledge, although they always avow that many things were by divine inspiration discovered and originated both by him whom they set up as their chief and leader and by our ancestors, nevertheless so commend their own diligence in investigating the structure of the organ of hearing and set it ahead of every one else's cleverness that they would have themselves and others believe attempts would be vain and labors idle on the part of those who might take the trouble to add something to or detract something from their discoveries; moreover, chief among their outstanding discoveries about the organ of hearing (for I have not now set out to write about every detail) is a certain cavity which they call the cochlea or blind passage, mainly for the reason that it consists of two or three spirals, like a snail's shell [cochlea], and has no opening as does that shell; they add that this cochlea is covered, like the natural cavities of teeth, with a certain very soft and very thin little membrane—it makes no difference whether this is a spread-out nerve or something else. Thus we are told by those on whom today are cast the eyes of all students of the faculty of anatomy. But I, who always approve and praise the writings of others that are worthy of praise and hold in greatest affection those who have deserved well of the art of medicine, have no reason to confirm what these men promise but by no means perform: I should like, to be sure, not to contradict them and much less to displease them, but Truth, than which nothing is more reverend in my eyes does not allow this: therefore, lest I appear to attack without reason those whom I love and respect, I shall not decide this question on my own judgment but shall submit it for decision, as if a controversial matter, to the eyes of the most famous anatomists and to the ears of all who do not spurn the labors of this art but willingly submit to them; for it does not escape me that spectators of dissections, who generally have sharp ears in every difficult matter, but duller eyes, are easily persuaded, and give assent to others; at last I approach the subject itself, which is to be explained in a few words.

No one would deny that the ossicles I mentioned a little while ago are moved with a certain motion, for they are seen to be so mutually connected and joined that their construction does not differ in nature from that of the other joints. But of what sort their motion is, or from what initial cause, or by what force it occurs, hardly any anatomist dares to explain. In this most agree, that the air, which while sounds are being emitted fluctuates like a wave, strikes the membrane stretched across the auditory passage, and then by a sort of progression from this membrane the ossicles are moved. But why, I beg, was it necessary, in order to accomplish this crude motion, for the all-wise Artisan of living creatures to show so great zeal and to be meticulous about the shape, articulation and position of these ossicles since, when the air rushes in, the membrane, which is like a drum, could without any such mechanism of organs be struck either by an ossicle or some more solid body of no artful elaboration? Certainly Nature, whom Hippocrates describes everywhere as just and not instructed by any one, does nothing without

φιλαυτία decipit, hæc Epistola, quæ Tua causa in lucem prodit, maximum eis injiciet desiderium & ardorem contemplandi Naturæ solertiam, atque admirabile artificium circa ea, quæ ab aliis, omni licet studio & labore ac diligentia investigata & perquisita, deprehensa tamen inventaque non sunt, ne ab iis quidem, diligentissimis alioqui & doctissimis Viris, qui sibi perfusum habent, nullum se locum inquirendi, nedum inveniendi, posterioribus Anatomicis reliquisse. Sed age rem ipsam aggrediamur.

Auditus Organa ab his Philosophis ac Medicis, qui primas tenent, negligenter admodum sunt descripta; nervum enim quinti jugi ex his, qui a Cerebro oriuntur, per meatum quemdam tortuosum procedere, & in membranam Aurium foramini obductam sese explicare ajunt, eamque, quoniam tenuis, sicca, & valde tensa est, ab aëre pulsatum, accedente ossium duritie, quæ eumenm cochleamve æmulantur, sonum efficere, sine alio Naturæ artificio, arbitrantur. Posteriores majore studio ejusdem Naturæ artem perscrutati, duo se parva ossicula in Lapidei Ossis caverna reperisse profitentur, quorum alterum quadratæ incudi, aut molari dentí appositissime, alterum malleo aut femori comparant, sed meo judicio parum apte; nam extrema pars femoris duabus apophysibus terminatur, ejusque caput superius & collum pro sua magnitudine parvum est, ut Galenus asserit, & sectio ipsa patefacit: sed ossiculi illius finis tenuis est & acutus, caput veto ita magnum, ut potior ipsius pars & crassior putanda sit. Horum sane ossium, quæ minima omnium sunt, nusquam Galenus, quod sciam, meminit; tametsi haud erant, ut quidam scribunt, ob exiguitatem negligenda, quum ipsorum usus non sit mediocris

cris, atque Ars summam Conditoris sapientiam in ipsis conformandis demonstret: dicat forsan aliquis, illa eum in libro de Motibus obscuris, quem temporis injuria amisimus, descripsisse; aut certe in libello de Ossibus innuisse, ubi in fine, quædam se ossicula consulto prætermisisse, dicit: verum prior conjectura levis admodum est, & rationi parum consona; posterior ratio haud omnino satisfacit, nam quemadmodum excusatione dignus videri potest, si in compendioso libro, cujusmodi est, qui de Ossibus inscribitur, exacte & minute omnia, & præsertim difficilia, non explicat, ita justa reprehensione carere nequit, quod in aliis Tractationibus longis & copiosis nullam de his ossiculis mentionem fecit. Cæterum, quantum ipse scio, hæc duo ossicula primi indicarunt Alexander Achillinus Bononiensis Philosophus insignis, & Jacobus Carpensis Chirurgus & Anatomicus non ita contemnendus, quamquam eum ingratissimi quidam postquam expilarunt, ut ab omnibus parvi fieret, Anatomicorum fœcem nominare non erubuerunt; neuter tamen eorum sibi tantum sumpsit, ut inventionis sibi palmam vendicaret. Qui eos secuti sunt, eorumdem ossium fabricam perinde scripserunt, ac si Naturæ industriam in eis conformandis perspectam ipsi ante omnes habuissent, quos tamen æquum erat in aliorum scriptis judicandis ita se præbere, ut homines intelligere non possent, majore eos diligentia & studio errata reprehendere, quam pulchra & utilia inventa laudare. Tertium ex his ossiculis, quod staffam aliqui seu stapedem appellant, in medio perforatum, superficie plana & inæquabili, figuraque triangula constans, posterius innotuit, de cujus quidem inventione hodie multi certant, nonnulli vero conscientia

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convicti, minime audent Inventorem justa laude fraudare; sed nituntur persuadere, neminem Medicum, ex iis præsertim, qui Romæ degunt, & Anatomen profitentur, id os cognitum habuisse eo tempore, quo illud ipsi in publicis Gymnasiis ostenderunt, & Johanni Philippo ab Ingrassia Siculo Medico ac Philosopho præstantissimo inventionis laudem tribuunt. Sed referat eam quisque, cui mavult, acceptam; ego quidem scio, me neque edoctum, neque monitum ab aliquo, multo antequam ipsi scribant, id ossiculum novisse, Romæque non paucis ostendisse, atque in æs incidendum curasse; fictaque nunc ex his, quæ explicaturus sum, ni fallor, manifestum, num propria ego industria Auditus Organa investigarim & invenerim; an potius aliorum opera usus, quæ ab illis recte inventa sunt, pro meis usurparim, & aliis recensere aggrediar.

Qui Anatomicæ hodie Artis Inventor, & quasi Architectus ab omnibus pene creditur, quintum nervorum Cerebri par, foramine admodum tortuoso, propria ipsius causa facto, in cavitatem Auditus Organo præparatam vehi, ibique varie discindi, ac propagines quasdam, ad similitudinem membranæ dilatatas, hujus cavitatis fedibus offerre, atque etiam Auditus Organi non infimam partem constituere asserit, nihil præterea addens, arbitratus hæc tantum esse, quæ circa Auditus Organa inventa & deprehensa sunt. Quæ quidem, & multa etiam alia, quæ ipse hac de re scribit, si æquo animo, veritatis indagandæ gratia, mecum expenderis, non dubito, quin a veritate abesse cognoscas, & in posterum multis in rebus fabricam ab eo scriptam suspectam habeas; quamvis enim aut communis beneficii, quod in Artem Medicam contulit, obtrectator, aut Virtutis hostis, aut

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laudis invidus nemo bonus esse debet, & ego semper præstantium Virorum imitatione, non invidia dignam esse, arbitratus sum; tamen eorumdem errata, quæ damnum afferre possunt, accurate demonstranda, & omni studio cavenda, ac declinanda esse puto; siquidem veritati amicitia præferenda non est, neque Personæ magis, quam Virtuti favendum; sed utrumque ab iis maxime fugiendum, qui honestorum bonorumque Virorum numero esse & haberi volunt: & ne maledicum me conviciatorem aliquis existimet, omnes Anatomiæ studiosos oratos esse velim, ut quæ ab eo Authore in octavo ac duodecimo capite primi libri, & octavo quarti scribuntur & pinguntur, attento antea animo legant, apertisque oculis intueantur; deinde orationem & picturam cum iis, quæ in dissectione manifeste apparent, deposita omni perturbatione animi, conferant; etenim certe scio, fore, ubi hoc sedulo effecerint, ut quæ antea maxima cum admiratione tanquam vera recipiebant, improbare statim incipiant: quisnam quæso hujus Artis peritus non reprehendat nervorum quinti jugi eorum, qui a Cerebro oriuntur, distributionem? quam ille, ut vere loquar, pro suo arbitrio confingit, & una cum osse temporum effracto pro voluntate pingit; quisque, obsecro, permittet ei in posterum, ut mirabili arte constructas Aurium cavitates, oratione ac lineis tam solute describat? quum (invitus, Deum testor, hoc dico) neque in oratione, neque in pictura veri quicquam insit; nimirum tres concavitates effingit, quarum una cornu parumper bis retortum, altera anguem in spiras mediocriter contractum, postrema vero rectum baculum aptissime referunt: sed nihil minus, quam Aurium cavitates ac meatus exprimunt.

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Fig. 3.—Pages 129 to 132 of the Epistle.

a reason but contrives the construction of each small part in keeping with the importance of its action and use, as the structure of the hand declares. The special use in arranging the joints of these ossicles I shall now disclose, that you may be able to contemplate and admire with me the skill and power of our Creator, which is plain even in the smallest things, and I shall point out how you can see this with your eyes, unless you are reluctant to carry out the labor of anatomy.

When Nature determined that the organs of hearing should be moved at will, she wished to bestow on them an articulation and a muscle, without which this motion cannot be produced: the form of the ossicles which serve the hearing, their number and arrangement have by now become known to almost everybody; but the muscle, so far as I know, nobody has yet discovered. If you desire to see it, opening the skull, cut into the bone which resembles a stone, in the place where it is hollowed out in a very shallow groove and projects forward toward the thinner base of the temporal bone, and remove its covering carefully, exerting the greatest caution not to injure the underlying organs. When indeed you have done this with expert hand, the muscle can be seen at once. Although it is the smallest of all, yet in elegance and intricacy of construction it yields to none; it rises from a substance resembling ligaments in the region where the bone that imitates a wedge is joined to the temporal bone, and leaving this point in fleshy form it gradually becomes somewhat broader as far as its middle; then, becoming narrower, it produces a very slender tendon, which is inserted into the greater process of the bone compared to a hammer [malleus] almost opposite the lesser process of the same bone; and in dogs, a little before the point of insertion, it has a fleshy round gland, somewhat depressed. This in dissection, to be sure, is difficult, but when one has undertaken it once or twice, one will find it easy. Nor is it possible, as one might think, by having recourse to larger animals, to see this artifice of Nature better in them than in Man; for, although they do not lack this muscle, it is found nevertheless much smaller in most of them than in Man, and more difficult to see, for the dimensions of individual parts have not always been assigned to animals as almost every one says, in proportion to their size; sometimes this does not hold, as we plainly see in the organ of hearing and certain other parts (which for brevity's sake I pass over). But the discovery of this tiny muscle, in which the supreme skill of Nature is evidenced, cannot help seeming to you highly important, unless you are prevented by envy and malevolence, since its knowledge opens a way not only of investigating how hearing is produced in us but also of judging how defective and imperfect on this point is the description given by others.

But to arouse far greater, or at least equal, admiration, I think I should disclose another example of the industry of our Creator in this same organ of hearing. The fifth pair of cerebral nerves by no means consists of only two nerves as others hold but has two unequal branches on each side, of which the greater is elegantly hollowed out lengthwise like a semicircle, and in friendly fashion takes in and embraces the lesser, a fact which has escaped others; and joined together in this manner both proceed obliquely forward and outward to the extremity of the pocket hollowed out for them in the bone resembling a stone; and here the lesser branch, separating from the larger, finds a small opening prepared for it, and enters, and by a very wonderfully twisted passage, of which it is not now convenient to speak, slips outside the skull; the larger branch on the other hand, seems to end in three portions slightly separated from one another, of which the chief is spread over a tiny opening which leads into the snail-shaped bone; but whether it merely lies on it like a cover, or really penetrates it deeply, and follows the convolution of this bone, I have not been able to find out for certain because of the difficulty of procedure. Moreover, this body which most elegantly resembles the shell of a snail is coiled into a circle with three convolutions, of which the broader occupies the upper position and receives the nerve, while the narrower occupies the lower position and ends in a hollow bone; and yet that bone ought not for this reason to be called, as some do, a blind cavity with no exit, since, although it has convolutions like the shell of snails, nevertheless it is not without an opening like those; but the center, in that portion, to be precise, on which the convolutions rest, is pierced from the beginning to the end by a narrow and straight passage; and from the opening in front of which is the triangular ossicle there is an open way which ends in the larger convolution of this bone; for if the cavity were blind, the air when struck could in no way reach the nerve. But since matters are as I have said, I myself think that air set in motion by the ear drum and the ossicles travels by the route I have set forth to the greatest convolution of the bone, and from there is reflected to the lesser, and thence ascends straight to the nerve by the opening in the middle.

I think that Empedocles was the first one to have an inkling of this wonderful device of our Maker, for, as Galen testifies in his book "His-

Poſteriores, quos novæ illæ omnium doctrinarum Inventrices Athenæ alunt, authoritatis & inventionis hujus Viri approbatores atque æmuli, quamvis multa divinitus, tum ab hoc, quem Principem & Ducem ſibi proponunt, tum a Majoribus noſtris inventa atque inſtituta eſſe, ſemper prædicent; nihilominus ſuam diligentiam, in Auditus Organi ſtructura inquirenda adeo commendant, cæterorumque omnium ſolertiæ præferunt, ut ſibi & aliis perſuaſum eſſe velint, vanos fore conatus, & inutiles labores illorum, qui operam dederint, ut inventis ſuis addant aliquid, aut detrahant: his autem, quæ præclare fuerunt ab illis circa Auditus Organa excogitata, (de ſingulis enim ſcribere nunc non inſtitui) cavitas quædam præcipua eſt, quam cochleam ſeu cæcum meatum ea maxime ratione vocant, quia duobus aut tribus gyris inſtar cochleæ conſtat, nullumque, veluti illarum teſtæ, exitum habet; addunt etiam hanc, quemadmodum naturales dentium cavitates, membranula quadam molliſſima ac tenuiſſima veſtiri, quæ an ſit nervus expanſus, an aliud, nihil referat. Hæc illi, in quos hodie oculi conjecti ſunt omnium Anatomicæ Facultatis ſtudioſorum. Ego vero, qui aliorum ſcripta laude digna probo ſemper & laudo, atque omnes de Medica Arte bene meritos ſummopere diligo, equidem cur ea, quæ hi pollicentur, & minime præſtant, confirmem, nihil habeo: vellem profecto eis non contradicere, multoque minus diſplicere, ſed veritas, qua mihi nihil eſt antiquius, hoc non patitur: ergo ne, quos amo & obſervo, arguere ſine ratione videar, hanc diſceptationem arbitrio meo non dirimam, ſed quaſi dubiam oculis clariſſimorum Anatomicorum, atque auribus omnium, qui hujus Artis

tis labores non aſpernantur, ſed libenter ſubeunt, judicandam ſubjiciam; neque enim me latet, diſſectionum ſpectatores, qui plerumque in rebus difficillimis aures habent acutas, oculos vero hebetiores, facile perſuaderi, & aliis aſſentiri: tandem ad rem ipſam aggredior brevibus explicandam.

Motu aliquo agitari, quæ paulo ante memoravi oſſicula, nemo inficiatur; ita enim invicem compoſita & alligata cernuntur, ut a cæterorum articulorum natura ipſorum ſyntaxis non diſcrepet: ſed qualisnam eorum ſit motus, quove principio, & qua vi fiat, vix aliquis Anatomicorum explicare audet; in hoc fere omnes conſentiunt, aërem, qui dum ſonus editur, tanquam unda fluctuat, membranam Auditorio meatui obductam pulſare, ab illa deinceps conſecutione quadam illa oſſicula moveri: at quid obſcero oportebat, ad hunc rudem motum obeundum, Sapientiſſimum animantium Opificem tantum ſtudium adhibere, & de horum oſſiculorum figura, articulatione, ac poſitione eſſe tam ſollicitum? quando aëre irruente, membrana, quæ tympano ſimilis eſt, ſine tali organorum apparatu percuti aut oſſiculo, aut aliquo ſolidiori corpore nulla arte elaborato poterat: nihil certo Natura, quam juſtam, & a nemine edoctam Hippocrates paſſim prædicat, ſine cauſa facit; ſed pro actionis, uſuſque præſtantia, ut manus fabrica declarat, conſtructionem quoque particularum molitur: quis autem in horum oſſiculorum articulis componendis præcipuus ſit uſus, ut Opificis noſtri artem ac potentiam, quæ vel in minimis elucet, contemplari ac mecum admirari poſſis, jamjam aperio; & quomodo oculis ipſam intueri poſſis, niſi ad ferendos Anatomiæ labores piger ſis, edocco.

Quum

Quum inſtituiſſet Natura Auditus Organa arbitrio voluntatis moveri, articulationem quoque ac muſculum, ſine quibus fieri is motus nequit, tribuere illis voluit: forma oſſiculorum, quæ Auditui ſerviunt, numerus, & compoſitio omnibus fere jam innotuit; muſculum, quod ſciam, nemo adhuc invenit, tu ſi illum videre cupis, aperta calvaria os incide, quod Petram refert, eo loco, quo linea minime alte penetrante exſculptum eſt, & verſus tenuiorem oſſis Temporis ſedem in anteriorem partem magis eminet, ejuſque ſquammam accurate detrahe, ſumma diligentia adhibita, ut ſubjecta organa nihil lædas: hoc ſane experta manu ubi efficeris, ſtatim muſculus conſpiciendum ſe exhibebit, qui etſi omnium minimus ſit, elegantia tamen & conſtructionis artificio nulli cedit; oritur a ſubſtantia ligamentis ſimili, qua parte os, quod Cuneum imitatur, cum Temporis oſſe committitur, indeque carneus evadens redditur ſenſim ad medium uſque aliquanto latior; deinde vero anguſtior effectus tendinem gracillimum producit, qui in majorem apophyſim oſſiculi Malleo comparati, fere e regione minoris apophyſis ejusdem, inſeritur; & in canibus, parum ante inſertionem, carneam rotundamque glandulam aliquantulum deprehendam habet. Hæc ſane ſectio difficilis eſt, ſed ubi quis ſemel aut bis eam obierit, facilem experietur; nec eſt, ut aliquis ad majora animalia confugiens arbitretur in illis melius, quam in Homine hoc Naturæ artificium intueri poſſe; quamvis enim hoc muſculo deſtituta non ſint, is tamen in pleriſque illorum longe minor, quam in Homine occurrit, & difficilius cernitur; neque enim ſemper, ut in ore fere omnium ſit, particularum moles animantibus pro ratione magnitudinis tributa eſt: ſed

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quandoque hoc fallit, ut in Auditus Organo, & quibusdam aliis partibus (quas brevitatis cauſa prætereo) plane perſpicimus. Cæterum exigui hujus muſculi inventio, in quo ſumma Naturæ Ars elucet, niſi invidia aut malevolentia prohibearis, non poterit tibi videri non magni facienda, quum ejus cognitio aditum patefaciat, tum perſcrutandi, quomodo Auditus in nobis fiat; tum vero judicandi, quam manca ſit hac parte aliorum deſcriptio, & imperfecta.

Sed ut longe majorem, aut certe parem admirationem moveam, faciendum puto, ut aliam Opificis noſtri induſtriam in hoc ipſo Auditus Organo aperiam. Quintum nervorum Cerebri jugum ex duobus tantum nervis, ut alii arbitrantur, minime conſtat, ſed duas utrimque propagines inæquales habet, quarum major ſecundum longitudinem, inſtar ſemicirculi, eleganter excavatur, minorem inque, quod alios fugit, amice ſuſcipit & amplectitur, eoque modo ambæ ſimul junctæ oblique in anteriorem & exteriorem partem, uſque ad extremum ſinus in oſſe Petræ ſimili earum gratia exſculpti, procedunt; ubi minor propago a majore recedens, parvum foramen ſibi paratum invenit, & ingreditur, mireque admodum flexuoſo inceſſu, de quo nunc loqui non eſt opportunum, extra calvariam elabitur; major autem propago videtur in tres portiones parum invicem diſtantes terminari, ex quibus præcipua exiguo foramine, in Cochleatum os pervio, obducitur: ſed num inſtar operculi eidem tantum incumbat, an vero alte penetret, & in ſpiras ejus oſſis convolvatur, propter difficultatem adminiſtrationis, certo explorare adhuc non potui: eſt autem id corpus, quod teſtam cochleæ elegantiſſime refert, tribus ſpiris in orbem convolutum, quarum elatior

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Fig. 4.—Pages 133 to 136 of the Epistle.

tory of Philosophy," he thought that hearing occurred by means of an impulse of the air which strikes a shell-like bone which is suspended within the ear like a bell. It seems that Aristotle also agreed with this, for he says at the beginning of the eleventh volume of the "Nature of the Animals" that the interior of the ear, similar to the curvature of a snail shell, terminates in a bone which imitates the shape of an auricle. It seems extraordinary to me that Empedocles was able to discover such a thing; even if he did not know of this device of Nature, it is much more to be wondered at that, concise as he was, he was able to portray that much by what he said, in spite of the fact that he knew nothing about it; indeed that which with few words explains accurately an obscure and greatly important thing commends the knowledge and diligence of the man.

I could say more about this thing which, as you have already heard, is far different than others describe it, if something else which I discovered did not compel me, before going beyond the limits of this treatise, to write something about it too, which certainly will bring to the practice of the medical art no moderate advantage. Even if it had little or no advantage, I would wonder because of the fact that even though it is situated before everybody's eyes and is such an easy thing to discover, yet it is either overlooked or negligently passed over by other anatomists. From the cavity of the petrous bone, then, in which the auditory passage called concha ends, a passage toward the nasal cavity is perforated; from that another passage begins like a small canal, as wide as a slender reed, which proceeding obliquely to the anterior and interior of the base of the head, penetrates and perforates the whole bone ending in the middle of four foramens, from the posterior of which the soporary [middle meningeal] artery enters the skull; from the anterior of which the fourth pair of cranial nerves come out; externally the artery which is distributed to the dura mater makes an entrance, and internally a certain fissure goes around, which is made by the extreme parts of the wedge-shaped bone and the petrous bone drawn together obliquely inward and to the front. Others would perhaps think that this passage, about which this dissertation is being written, ends in that place; this is not so, however, for it is augmented by a substance of different nature and is carried on between two muscles of the pharynx, up to now known to very few, along the fissure which I mentioned a little while ago, and it ends in either cavity of the nose near the internal part of the root of the apophysis of the bone that is shaped like the wings of a bat, and is inserted in the thick revestment of the palate near the root of the uvula. Its substance, where it touches the extremity of the fissure which is common to the temporal and wedge-shaped bones, is cartilaginous and quite thick; but the substance of the opposite part is not exactly cartilaginous, but is somewhat membranous and becomes thinner gradually; but the internal end of this passage, facing the middle of the nasal cavity, has a strong cartilage, which is very thick and is covered by the mucous membrane of the nares, and is seen at the end of the same meatus as if it were a guardian. It is not round, but is somewhat depressed and makes two angles: it is as large as a writing cane, but is twice as large at the end as at the beginning, which is equally invested by a mucous membrane which is, however, thinner.

This extraordinary device of Nature, which I discovered, should not be overlooked, for it could be of no small advantage to philosophers and to doctors alike; indeed the older philosophers, among whom I mention Alcmæon, as Aristotle mentions at the beginning of the eleventh volume of the "Nature of the Animals," thought that goats breathe not only through their mouths and noses but also through their ears, because they did not overlook the important passage which I described, but rather often demonstrated experimentally that when one holds his breath the air returns to the cavity of the ears, pushed by a certain force, and strikes the organs of hearing like a flood. The knowledge of this passage could be of great use to doctors for the proper employment of medicines, for henceforth they would know that thick substances could easily be expelled not through narrow foramens but through a wide passage, either by nature or with the help of medicines which are called "masticatory."

Even if anybody thinks that the advantages I have just mentioned are of no moment and ignores this passage altogether, looking carefully for another goal of nature in shaping the organs of hearing, he should be greatly moved and should admire the art and knowledge of the Great Creator, who does nothing uselessly. The nerve to the tympanum and the organs of hearing could have been distributed easily from one or the other part of the fifth pair of cranial nerves; but we see that this is not so, for a small offshoot from the branch of the fourth pair of nerves of the same viscus enters the cavity of the ears after having turned back and proceeded along the bony canal which I have just described, and it adheres obliquely to the tympanum and finally to the malleus, above the insertion of the muscles. It does not end, however, but proceeding farther it perforates the petrous bone in the posterior portion of the

ſuperiorem obtinet ſedem, & nervum ſuſcipit; anguſtior vero inferiorem, & oſſis cavo terminatur; neque tamen eſt hanc ob cauſam, uti quidam faciunt, os iſtud cæca cavitas exitum non habens appellandum, quia, etſi in modum teſtæ cochlearum ſpiras habet, nihilominus foramine, veluti illæ, non caret; ſed in medio, ea nimirum parte, cui ſpiræ innituntur, a principio ad extremum uſque, anguſto & recto meatu eſt pervium, & ab eo foramine, cui triangulum officulum præeſt, via aperta eſt, quæ in majorem hujus oſſis ſpiram definit: etenim ſi cavitas cæca eſſet, percuſſus aër nervo occurrere nullo modo poſſet. Sed quia ita, ut dixi, res ſe habet, arbitror ipſe aërem a tympano, & ab officulis agitatum eo, quo expoſui itinere, ad majorem oſſis ſpiram pervenire, indeque ad minorem reflecti, mox per medium foramen rectum ad nervum aſcendere.

Nec ſilentio prætereundum eſt, os Cochleam referens ex duplici ſpirarum genere conſtare, quorum alterum, a nobis jam expoſitum, ab oſſea ſubſtantia admodum tenui, ſicca, & quæ facile teritur, creatur; alterum vero, omnibus Anatomicis adhuc ignotum, ex materia quadam fit molli & mucoſa, firma tamen, & quæ neſcio quid arenoſi permixtum habet, oriturque ex medio ſpacio priorum ſpirarum, tanquam ex ampliore baſi, ſenſimque extenuatum in aciem definit; ſed non tam alte conſcendit, ut oſſis ambitum, qui priores ſpiras terminat, attingat. Comparari poteſt appoſitiſſime ejus forma teſtæ cochlearum, exteriore prius ex ea ſuperficie rotunda detracta, & parte interiore, quæ in ſpiras contorquetur, reſervata: qua autem ſubſtantia poſteriores hæ ſpiræ efficiantur, fateor me ignorare; quamvis non parvi referre arbitrer ſcire, nervusne

ipſe aliquam ejus portionem conſtituat, an minus. Hanc miram Opificis noſtri induſtriam, primum omnium innuiſſe Empedoclem ſuſpicor; quum, ut teſtis eſt Galenus in libro de Hiſtoria Philoſophica, Auditum impulſione ſpiritus fieri docuit, qui os cochleæ ſimile intra Aurem tintinnabuli inſtar ſuſpenſum percutit atque pulſat, cui etiam Ariſtoteles aſſentire videtur, aſſerens primo de Natura Animalium undecimo, partem interiorem Auris, forma anfractui cochleæ ſimilem, deſinere in os, quod auriculam plane imitatur. Mirum certe mihi videtur, Empedoclem hoc inveniſſe; ſed ſi hanc Naturæ artem etiam ipſe ignoravit, ut quispiam forte putaverit, (ejus enim oratio brevis admodum eſt & conciſa) multo magis mirandum eſt, quum eam neſciret, dicendo ipſum tantum poſſe; id enim doctrinam hominis ac diligentiam præcipue commendat, quod paucis, ſed propriis verbis, rem occultam magnique momenti accurate explicat.

Plura poſſem hac de re dicere, quam, ut jam audiviſti, longe ſecus, quam alii ſcribunt, ſe habere conſtat, niſi aliud noſtrum inventum me compelleret, ut antequam hæc tractatio Epiſtolæ limites pertranſiret, aliquid etiam de eo ſcriberem, quod certe ad Medicam Artem exercendam non mediocrem utilitatem afferet, tametſi nihil in ſe artificii, aut parum certe, habet, ſolumque eam ob cauſam movere admirationem poteſt, quod cum ante omnium oculos poſitum ſit, & inventu facile, a cæteris tamen Anatomicis, aut plane contemnitur, aut negligenter prætermittitur. Ergo a caverna Oſſis lapidei, in quam Meatus Auditorius, Conchion appellatus, finitur, via in Narium cavitatem perforata eſt; ab illa enim Meatus alter oritur rotundo

canaliculo ſimilis, & inſtar tenuioris calami amplus, qui oblique ad anterius interiuſque baſis capitis latus procedens, in medio quatuor foraminum totum iſtud os penetrat atque perfodit; nam poſteriori ipſius ſede arteria ſoporaria Calvariam ingreditur; anteriori quartum nervorum Cerebri jugum extra ipſam emergit; externum latus arteriæ in duram Cerebri membranam diſtributæ aditum patefacit; internum denique fiſſura quædam circumſcribit, quæ a cuneum referentis ac lapidei Oſſis extremis partibus, oblique infra & ante ductis, fit. Cæterum hunc Meatum, de quo ſermo eſt, arbitrabitur fortaſſe quispiam eo loco deſinere; res autem non ita ſe habet, ſed alterius generis ſubſtantia auctum, inter duos faucium ſeu gulæ muſculos, a paucis hucuſque bene cognitos, ſecundum paulo ante memoratæ fiſſuræ ductum ulterius procedit, & juxta radicem internæ partis apophyſis Oſſis, Alis Veſpertilionum ſimilis, in alteram Narium cavitatem terminatur, & in craſſam Palati tunicam prope radicem Gargareonis inſeritur. Subſtantia ſane ejus, qua extrema fiſſuræ oſſi Temporum & Cuneo ſimili communis tangit, cartilaginea eſt, ac admodum craſſa; huic vero oppoſitæ partis ſubſtantia exacta cartilago non eſt, ſed membranoſum neſcio quid habet, & tenuior evadit: at hujus Meatus interna extremitas, Narium cavitatis medium reſpiciens, robuſta eſt cartilago, quæ plurimum extuberat, mucoſaque Narium tunica obducitur, ac fini ejusdem Meatus quaſi Janitor præfecta eſſe videtur: figura teres non eſt, ſed aliquantum depreſſa duos efficit angulos: latitudo cavitatis calamum, quo ſcribimus, fere adæquat, ſed in fine duplo latior eſt, quam

in principio, quæ ſimiliter mucoſa, ſed tenui induitur tunica. Hoc callidiſſimum Naturæ artificium a me inventum contemni (ut opinor) non debet; ſiquidem tum Philoſophis, tum Medicis non parum utilitatis afferre poteſt; nam antiquiores Philoſophi, quorum numero, ut Ariſtoteles refert primo de Natura Animalium undecimo, fuit Alcmæon, capras non modo Ore ac Naribus, verum etiam Auribus quoque ſpirare, forte ob eam cauſam arbitrati ſunt, quod Meatum, quem deſcripſi, non ignorarent, atque adeo ſæpius experti fuiſſent, ſpiritum, ubi ipium quis cohibet, ad Aurium cavitatem vi quadam impulſum recurrere, & inſtar fluctus Auditus Organa percutere. Erit etiam Medicis hujus Meatus cognitio ad rectum Medicamentorum uium maxime utilis, quod ſcient poſthac ab Auribus, non anguſtis foraminibus, ſed ampliſſima via poſſe materias etiam craſſas, vel a Natura expelli, vel Medicamentorum ope, quæ maſticatoria appellantur, commode expurgari.

Quodſi quispiam, quas modo narravi utilitates, nullius momenti cenſuerit, atque ejusmodi Meatum plane contempſerit, is alium Naturæ ſcopum in conformandis Auditus Organis diligenter contemplatus, vehementer animo fortaſſe commovebitur, & ſummi Opificis artem ac ſapientiam, qui nihil fruſtra facit, admirabitur, maximisque laudibus extollet. Poterat ſane ad Tympanum, & ad Organa Auditus, ab una aut ab altera portione quinti paris nervorum Cerebri, commode nervus diſpenſari; quod tamen minime factum fuiſſe cernimus, ſed ab altero ejusdem Viſceris quarti jugi nervorum ramo exilis quædam propago, re-

Fig. 5.—Pages 137 to 140 of the Epistle.

auditory meatus, then reflected dorsally, continues for a while and finally unites with the thinner and harder branch of the fifth pair of cranial nerves. The other anatomists did not know of this smart and wonderful device of nature; indeed a good number of them who are thought to be foremost today at times recommend so much their accuracy in the study and description of these nerves that they think there is hardly anything that could be added to it; yet at times they affirm that this nerve, which they call a thread or a very thin chord, transverses the tympanum, but they not only do not say wherefrom it originates and how it proceeds, but, altogether forgetful of their accuracy which they otherwise had commended, very simply confess not to know whether it is an artery or a nerve.

These are the things, most honorable Frances, which I thought should be explained about the auditory organs, having omitted purposely a good many things, so that those who practice with great care this art today could have a chance of discovering better and more beautiful things and teach them, a thing which I will soon do, with God's consent. For the present it is enough for me to know with what ingenuity Nature constructed and fortified the auditory organs, and in what way It wanted the voice to reach the brain after having been slowly and gradually modified through various concavities and spirals: as if It [Nature] warned everybody not to assent easily to a speech without premeditation and mature judgment, especially when the honor and dignity of somebody is being detracted. But to you who judge according to this principle all you hear from jealous and ill-willing persons, again and again I pray not to stop loving and protecting me in the future. Be well. Rome, October 19, 1562.

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flexo itinere juxta illum, quem modo deſcripſi, oſſicum canalem, Aurium cavum, in quo oſſiculi Auditus continentur, ingreditur, & oblique Tympano, ac deinde oſſiculo malleum imitanti ſupra muſculi inſertionem adhæreſcit, nec ibi deſinit, ſed ulterius procedens Os lapideum in poſteriori ſede Meatus Auditorii perforat, deorſumque reflexa parumper repit, ac tandem cum tenuiori durioriquc ramo quinti paris nervorum Cerebri jungitur, & coit; hanc ſane callidam, miramque Naturæ ſolertiam cæteri Anatomici ignorarunt; quamvis plerique illorum, qui primas hodie tenere putantur, in horum nervorum inveſtigatione, atque deſcriptione, modo ſuam diligentiam adeo commendant, ut vix aliquid addi poſſe exiſtiment; modo hunc nervum, quem filum, ſeu chordam tenuiſſimam vocant, per medium Tympanum percurrere aſſerunt, ſed unde is oriatur, & qua incedat, non ſolum taceat, verum etiam, num ille nervus ſit, an arteriola ſuæ, quam alias tantopere commendaverant, diligentiæ obliti, ingenue ſe ignorare fateantur.

Hæc ſunt, Ornatiſſime Franciſce, quæ nunc de Auditus Organis explicanda duxi, plurimis conſulto prætermiſſis, ut qui hanc Artem hodie diligentiſſime excolunt, occaſionem habeant meliora, & pulchriora inveniendi, atque docendi, id quod me quoque, annuente Deo, brevi effecturum polliceor: ſatis mihi fuit in præſentia aliqua ex parte indicaſſe, qua ſolertia Auditus Organa Natura conſtruxerit atque munierit, & qua conditione vocem per varias concavitates ac ſpiras, quaſi per diverſos gradus, ſenſim elaboratam, & quodam modo fractam, in Cerebrum ipſum aſcendere voluerit;

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erit; quaſi omnes tacite admoneat, ne orationi, quæ eſt animi nuncia, ſine diligenti præmeditatione maturoque judicio, præcipue quando honori & dignitati alicujus detrahitur, facile aſſentiendum ſibi proponant: Te vero, qui hac ratione ea, quæ ab invidis ac malevolis audiveras, judicaſti, etiam atque etiam oro, ne me amare ac protegere in poſterum quoque deſiſtas. Vale. Romæ quarto idus Octobris. M D LXII.

Fig. 6.—Pages 141 and 142 of the Epistle.

Fig

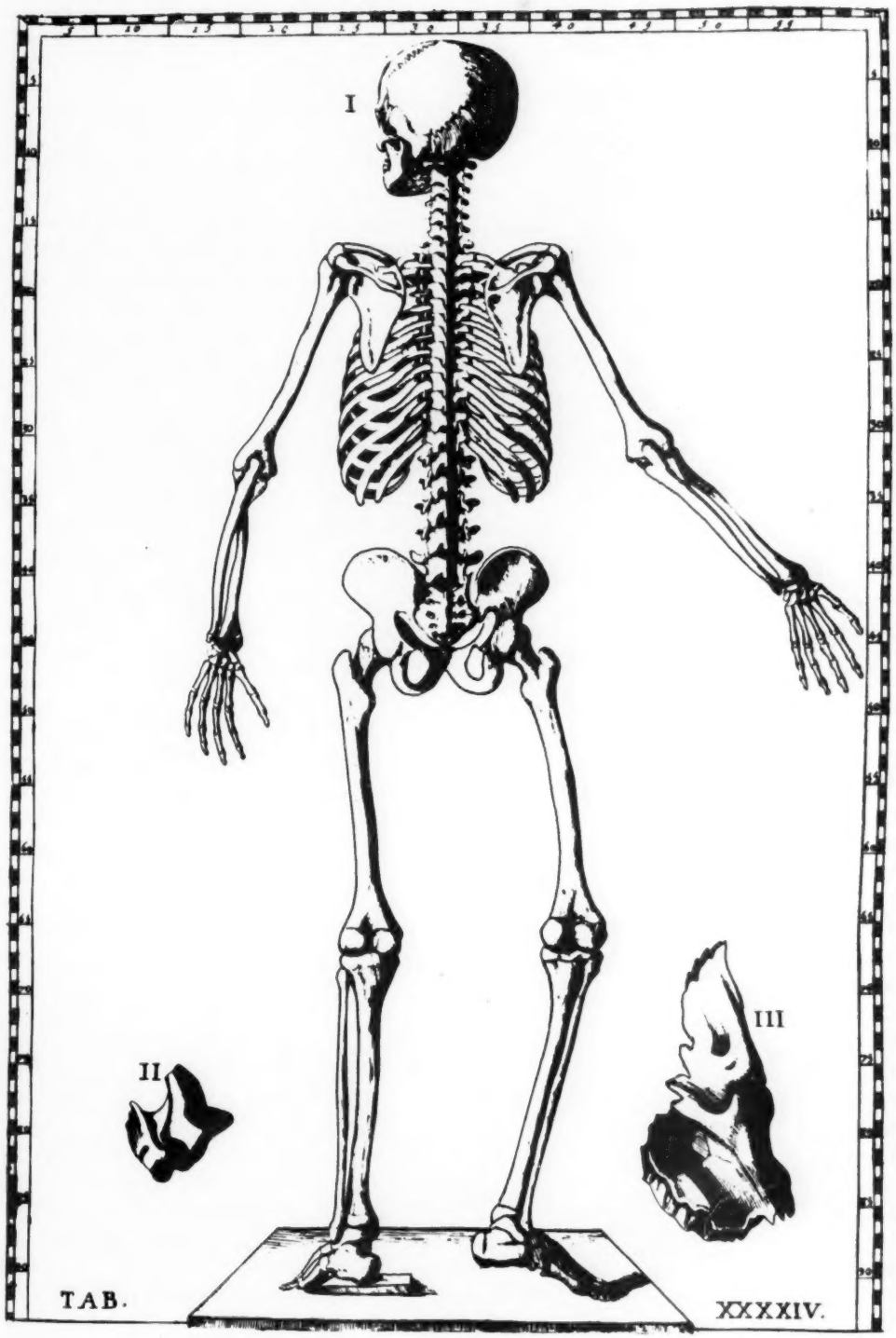

Fig. 7.—*I*, skeleton, back view; *II*, section through the external auditory meatus; *III*, petrous temporal bone.

CARCINOMA OF THE LARYNX

A REVIEW OF TREATMENT AND END RESULTS AT THE BROOKLYN CANCER INSTITUTE

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BROOKLYN

The most significant prognostic factor in any case of laryngeal carcinoma appears to be the exact site of origin of the lesion. The significance of this factor seems to be due to the fact that the supporting matrix beneath the mucosal surface of the vocal cords is made up of a dense fibrous connective tissue with little or no lymph drainage while the supporting structure beneath the epithelium of the extrinsic larynx is that of a loose areolar tissue rich in lymph supply (Lore [1]). In most cases an epithelial new growth arising in or about the larynx is squamous cell carcinoma. It is true that there is a variation as to maturity of structure and that acanthoma more usually arises on a vocal cord. Harris and

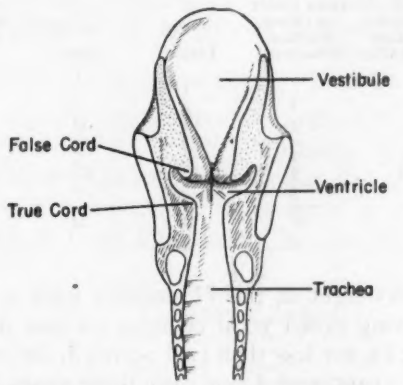

Fig. 1.—Laryngeal air passage as seen in a coronal section.

Klemperer [2] stated that "histologic structure is of minor importance in determining the radiosensitivity of laryngeal carcinomas." It is therefore more the character of the framework and the richness of the lymph drainage which affect most the progress and spread of these neoplasms. As a corollary, the rapidity of growth, the manner of spread, the prognosis and the modality of treatment vary markedly with lesions which arise within a few millimeters of each other (figs. 1, 2 and 3).

1. Lore, J. M.: Practical Anatomical Considerations of the Larynx, Laryngoscope **43**:693-717, 1933.

2. Harris, W., and Klemperer, P.: Pathologic Differentiation Between Radiosensitive and Nonradiosensitive Malignant Neoplasms of the Larynx, Arch. Otolaryng. **28**:355-363 (Sept.) 1938.

STATISTICAL REVIEW

The cases of all patients with laryngeal carcinoma who were admitted to the Brooklyn Cancer Institute from 1934 through 1942 have been reviewed. This paper represents a study of (1) the symptoms, (2) the classification, (3)

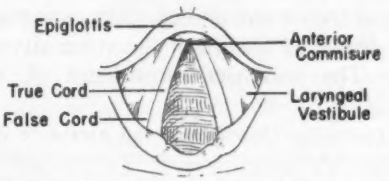

Fig. 2.—The larynx as seen from above.

the pathologic changes, (4) the methods of treatment and (5) the results obtained in these cases. The percentages of patients surviving are calculated as described without deletion except when pathologic demonstration of the disease was not obtained. Cases are listed according to the

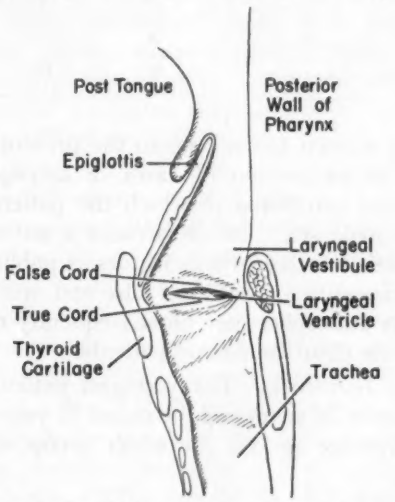

Fig. 3.—Laryngeal air passage as seen in a sagittal section.

year of admission of the patient to the Brooklyn Cancer Institute. The operative procedure may have antedated the admission of the patient to the institute in several instances. The period of survival, however, is measured from the date on which therapy was first instituted.

Seventy-seven persons with laryngeal carcinoma were admitted to the Brooklyn Cancer

Institute from 1934 through 1942. The patients treated in 1943 are not included, as a follow-up period of twelve months or less can hardly be deemed to furnish conclusive evidence of a successful result. The data on 6 of these patients are deleted for reasons which will be stated later in this review.

Sex Incidence.—Only 3 of the entire series of patients were females. Of the females, 2 are recorded as having lesions arising in the intrinsic, and 1 a lesion in the extrinsic, larynx (postcricoid).

The high incidence in males suggests some possible intrinsic etiologic factor in testicular hormone. Certainly, testicular hormone must be considered as dominant in the control of the growth of the larynx and of other changes, shown by the deepened timbre of the voice after adolescence. The increased prevalence of smoking among women has not up to the present altered the high proportion of cases of laryngeal and bronchial carcinoma in which the patients were of the male sex. In all fairness it must be admitted that such extrinsic factors as public speaking, exposure in outdoor jobs and working in a dusty atmosphere are more frequently recorded for male than for female patients.

Age Incidence.—The youngest patient in the series was 38 years and the oldest 81 years of age. The average age for the whole group was 58½ years.

TABLE 1.—*Distribution of Cases with Regard to Year of Admission, the Treatment and the Result*

		Treatment				End Result		
Year	Cases	Operation	Irradiation with More Than 4,875 r	Operation and Irradiation with Less Than 4,875 r	Palliative Irradiation with Less Than 4,800 r or Other Surgical Treatment	Living	Dead	Average Survival Period, Mo.
1934	1	1	..	..	..	..	1	87
1936	3	1	2	..	..	1	2	3
1937	10	1	7	..	2	3	7	7
1938	11	1	5	1	4	1	10	12
1939	13	1	10	..	2	3	10	11
1940	12	2	6	3	1	5	7	5
1941	13	2	7	2	2	1	12	20
1942	8	1	6	..	1	3	5	5
Total	71	10	43	6	12	17	54	13

STUDY OF SERIES UNDER CONSIDERATION ACCORDING TO YEAR OF ADMISSION

The distribution of the cases according to the year of admission and the result obtained are given in table 1.

SYMPTOMATOLOGY

The earliest symptom of laryngeal cancer is usually a "husky voice" (Clerf[3]). Ulceration limited to a vocal cord may not produce pain. The first indication of carcinoma arising in the extrinsic laryngeal structures may be dysphagia. This is most probably due to the carcinoma's rapid permeation of the surrounding lymphatics. Enlargement of cervical lymph nodes is common in patients who present themselves with a primary cancer arising in the vicinity of a vocal cord. With the extrinsic growth, when ulceration is present, pain may antedate the vocal changes. The pain is aggravated by swallowing and tends to simulate that of persistent sore throat. As the neoplasm extends the voice changes are progressive: from huskiness the phonation deteriorates into a harsh whisper and may progress even to aphonia. The patient who is aphonic usually has partial obstruction of the airway, as shown by dyspnea, orthopnea and even cyanosis.

Forty-eight of the 71 patients gave a history of having noted vocal changes for less than one year; 14, for less than two years; 3, for less than three years, and 3, for over three years. There were 3 patients for whom the duration of this symptom was not recorded.

In spite of the fact that the greater number of patients gave a history of hoarseness of less than one year, most of the lesions were far advanced when first examined at the Brooklyn Cancer Institute. This is illustrated by the fact that surgical intervention, except emergency tracheotomy, was carried out in only 17 instances.

CLASSIFICATION

(*a*) Carcinoma of the intrinsic larynx usually originates on the free edge of a vocal cord. According to Hammond,[4] it may also occasionally arise on the "ventricular bands" or in the interarytenoid region." The neoplasm is usually of the squamous cell variety. Due to its location,

3. Clerf, L. H.: Hoarseness and Cancer of the Larynx, West. J. Surg. **49**:599-602, 1941.

4. Hammond, A. E.: Diagnosis and Treatment of Cancer of the Larynx with a Statistical Review of Fifteen Cases, Arch. Otolaryng. **35**:1-29 (Jan.) 1942.

epithelioma arising on the free edge of a vocal cord spreads by direct contiguity along the surface of the cord. It usually bridges the anterior commissure before extending into the nearby lymphatics.

(*b*) Carcinoma of the extrinsic larynx takes origin most frequently on the epiglottis, the aryepiglottic folds or the arytenoids, within a piriform sinus or along the posterior laryngeal wall. Hammond [4] stated that "the upper border of the ventricular bands, merging into the aryepiglottic folds, must be included in the extrinsic area." Carcinoma arising in the extrinsic structures about the true larynx is also most frequently of the squamous cell type. With the rich lymphatic framework about the hypopharynx, it metastasizes early into the cervical lymph nodes (Lenz [5]). In this series many of the patients with a lesion arising in the extrinsic larynx had enlarged cervical lymph nodes on admission; most of the enlargements were certainly due to carcinoma. When a tumor arises on the anterior wall of the hypopharynx, it is often referred to as "postcricoid" in location and, because of this location, is often classified with the pharyngeal or esophageal lesions.

PATHOLOGY

In the eight year interval between Jan. 1, 1934 and December 31, 1942, 77 patients were admitted to the institute with a diagnosis of carcinoma of the larynx. The cases of 6 of them are deleted from this survey for the following reasons: in 4 instances there was neither pathologic proof of the correctness of the diagnosis, nor follow-up examination; in 1 instance there was no pathologic proof because of early death; in 1 instance, though the patient survived after roentgen therapy, there was no pathologic proof of the presence of cancer. There remained 71 cases with pathologic proof and follow-up observations to the time of writing. In each of these 71 cases there was a biopsy record of carcinoma. This group of proved cases of laryngeal carcinoma have been followed as to end result to the time of writing—February 1944. The follow-up interval therefore extends from one to nine years.

TABLE 2.—*Pathologic Classification of Seventy-One Cases of Laryngeal Carcinoma*

	Total	Squamous Cell Carcinoma	Anaplastic Carcinoma	Adenocarcinoma	Unclassified
Intrinsic	35	30	2	0	3
Extrinsic	36	32	3	1	0

The pathologic classification is given in table 2.

METHODS OF TREATMENT

When carcinoma is localized, operation offers the greatest opportunity for cure, and it is therefore the policy at the Brooklyn Cancer Institute to excise the growth when possible. Lesions too advanced for excision are usually referred for radiation therapy (Martin [6]). This program is carried out with the complete agreement of the members of the radiologic staff, who appreciate the curative value of surgical removal in suitable instances. All patients with nonoperable carcinoma are accepted for radiation treatment, appreciating that in many instances irradiation of the cancer is in no sense a curative procedure and can be considered as of only slight benefit, being used to reduce edema, pain or infection.

Two modalities of treatment therefore, are offered: (*a*) surgical treatment and (*b*) radiation therapy. Both surgical and radiation treatment can be subdivided into palliative and curative procedures.

PALLIATIVE PROCEDURES

Tracheotomy and gastrostomy are performed only for relief of symptoms due to pressure and cannot therefore be considered as in any sense curative. These operations are classified along with small doses of roentgen radiation under the heading of "palliative procedures." Thirty-six patients underwent tracheotomy and 2 gastrostomy. Many of the tracheotomized patients were later treated with roentgen radiation. It is our experience at the Brooklyn Cancer Institute that tracheotomy should be limited to patients requiring airway as an emergency inasmuch as roentgen therapy will often reduce edema and stridor. Tracheotomy is always followed by a certain amount of local infection plus pneumonia due to aspiration. Both these complications can mitigate against the patient's tolerating therapeutic doses of roentgen radiation. Five of the survivors were tracheotomized in the course of their treatment.

CURATIVE SURGICAL PROCEDURES

Four types of surgical treatment were carried through in this series: (*a*) electrocoagulation, (*b*) epiglottic resection, (*c*) laryngofissure, (*d*) laryngectomy. Surgical procedures are performed on selected patients, which should give

5. Lenz, M.: Radiation Therapy of Cancer of the Larynx, in Pack, G. T., and Livingston, E. M.: Treatment of Cancer and Allied Diseases, New York, Paul B. Hoeber, Inc., 1940, vol. 1, p. 560.

6. Martin, H. E.: Selection of Treatment for Cancer of the Larynx, Ann. Otol., Rhin. & Laryng. **49**:728-735, 1940.

this group a certain advantage as to end result. All of the surgical procedures except electrofulguration and epiglottic resection were performed on patients whose cancer arose in the intrinsic larynx.

Electrocoagulation.—Three patients received electrocoagulation directed to an extralaryngeal growth. Recurrence followed fulguration in each instance. One in three is living at the time of writing, without evidence of disease.

B. F., admitted in 1940, repeatedly received fulguration of the epiglottis. The cancer recurred immediately, and roentgen radiation, 6,600 roentgens (r), was delivered to the lesion. He is alive without evidence of disease.

V. P., admitted in 1940, received a full cycle of roentgen therapy, 6,200 r being delivered to the larynx. This was followed by fulguration, recurrence and then further large doses of roentgen radiation to the larynx and upper mediastinum. She died fifteen months after treatment by cautery.

C. K., admitted in 1940, also received roentgen radiation, 5,200 r, to the larynx, followed by cauterization of the epiglottis and then some further roentgen therapy. He died of recurrence four months after cauterization.

Epiglottic Resection.—One patient was so treated. The tumor arose in the extrinsic larynx.

J. G., admitted in 1939, underwent roentgen therapy, 6,000 r delivered to the larynx, for a growth arising at the base of the epiglottis. The epiglottic resection was performed three months later because of chondritis. No carcinoma was found on microscopic examination of the removed epiglottis. Over a year later carcinoma of the buccal mucosa developed in this patient. It also was destroyed by roentgen radiation. The carcinoma of the larynx was classified as squamous cell and that of the buccal mucosa, as adenocarcinoma. The patient is living and well without evidence of disease.

Laryngofissure.—Laryngofissure was performed on 9 patients whose cancer arose in the intrinsic larynx. One died of complication seven years after operation. Five are living at the time of writing; one of these has received radiation therapy for recurrence.

B. M. was admitted in 1934 for laryngeal carcinoma. In 1941 (seven years after operation) he died of heart disease without evidence of recurrence of his carcinoma.

H. B., admitted in 1936, is alive at the time of writing, without recurrence.

Two patients who were admitted in 1937 are both alive and well without recurrence: M. S. received preoperative irradiation of the tumor (3,300 r). In the case of J. G. biopsy one year after laryngofissure revealed recurrence of the growth. He received 5,000 r to the larynx two years after operation. This case is therefore listed in the tables under radiation therapy.

H. O., admitted in 1940, is alive without recurrence. No roentgen therapy was given.

Three patients were admitted in 1941. All have died: S. K. had undergone laryngofissure twelve years before in another city. He died of recurrence. I. L. died of recurrence in 1943, two years after operation. L. B. died in 1941. His laryngofissure had been performed in another institution in 1940. This patient was treated in 1941 by gastrostomy. He died of recurrence, having survived seventeen months.

M. C., admitted in 1942, is living without recurrence.

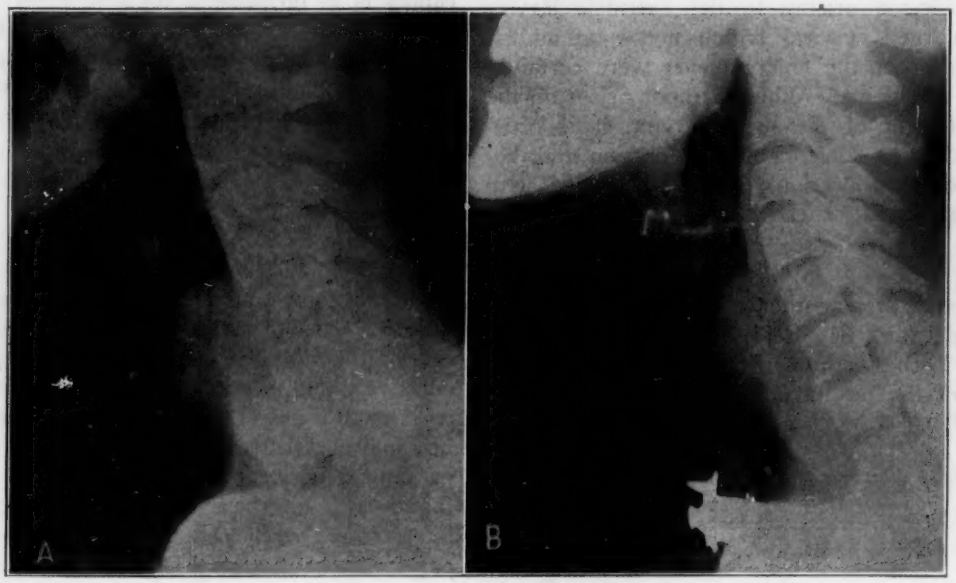

Fig. 4.—*A*, roentgenogram of J. H., a white man aged 41. He was admitted to the hospital Dec. 4, 1936. A tumor mass with an ulcer at its base involved the epiglottis. Biopsy proved it to be epidermoid carcinoma. Tracheotomy was performed December 5. Roentgen therapy was given from Dec. 9, 1936 to Jan. 16, 1937. *B*, roentgenogram of the same patient after tracheotomy and treatment with roentgen rays, showing marked reduction in the tumor of the epiglottis and establishment of a more normal airway. The patient, however, died Dec. 3, 1937 of recurrence and extension of the carcinoma.

Laryngectomy.—This operation was performed on 5 patients. In each the cancer arose in the intrinsic larynx. Two patients are living without evidence of disease.

M. L. survived but forty-eight hours after admission to the hospital in 1938. He had undergone tracheotomy in May 1937, followed three weeks later with laryngectomy in another institution. He lived in all about ten months following laryngectomy.

L. B. died of recurrence in the year of his admission to the hospital (1938). Laryngectomy had been performed in 1931 and radium applied in 1937. These procedures were carried out in other institutions.

W. S., admitted in 1939, is alive and well without recurrence at the time of writing. He received a small amount of roentgen therapy preoperatively.

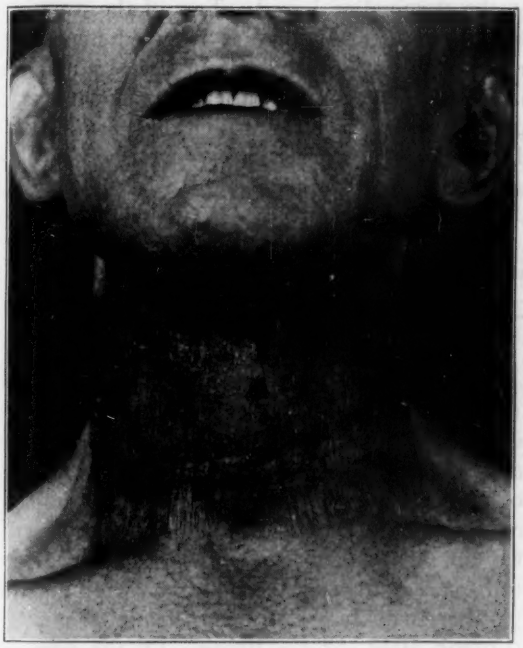

Fig. 5.—Reaction to radiation following delivery of 6,050 r to the larynx. The patient (W. P., table 3) is living without evidence of disease almost six years after completion of the treatment.

S. H., admitted in 1940, is alive and well without recurrence. His carcinoma received no radiation.

N. R. was laryngectomized in 1941; this was followed by recurrence. The growth received 5,000 r and repeated doses of radon seeds. The patient died of extension of carcinoma and metastases some two years later.

CURATIVE RADIOTHERAPY

Both radium and roentgen rays have been used in the treatment of laryngeal carcinoma. The treatment with radium can be delivered as teleoradium therapy. This requires large quantities of radium and at best is difficult to apply because of the bulk and weight of the radium container. Radium can be applied in the form of needles or gold implants for interstitial therapy. Such insertion produces trauma to the part, and with any interstitial application the evenness of the distribution of the sources of radiant energy depends a great deal on the individual skill of the operator and the location and the extent of the growth. Overirradiation of cartilage (Lenz [7]) results in chondritis, chondronecrosis and long-standing disability if not death from bronchial pneumonia. Ingenious intubation tubes have been prepared for intralaryngeal application of radium (Stupka [8]). Up to the present, none of these radium procedures appear to have any advantage over treatment with high voltage roentgen rays (figs. 4, 5 and 6).

Roentgen therapy is chosen in this institute as the more efficient modality for irradiation of laryngeal carcinoma. All patients treated at the Brooklyn Cancer Institute have received roentgen radiation, a modified Coutard [9] type of repeated daily doses being given, with the dose calculated in the manner described by Howes and Bernstein.[10]

Fifty-four of the 55 remaining patients received roentgen therapy. Patients receiving this therapy can therefore be considered as those with intrinsic lesions which were considered too extensive for surgical treatment and most of those with extrinsic growths which, as a rule, are not amenable to surgical treatment in any stage. Many were admitted in such an advanced state of disease that but small palliative doses of roentgen therapy were given in the hope of reducing edema or infection. Therefore, for the study of end results it was decided to subdivide these patients into two groups: (1) those who received 4,875 r or more to the tumor in one continuous cycle of not over seven weeks' duration (Paterson [11]) and (2) those who received any dose of roentgen radiation up to 4,875 r, obviously not a carcinogenic dose.

According to this postulate, 43 patients received a so-called therapeutic dose. Twenty-four of these 43 patients are listed as having a neoplasm that arose in the extrinsic larynx and 19 one that arose in the intrinsic larynx. Ten, or 23.25 per cent, of the 43 patients who

7. Lenz, M., in discussion on Symposium on the Treatment of Carcinoma of the Pharynx and Larynx, Radiology **34**:161-163, 1940.

8. Stupka, W.: Ein allseitig im Kehlkopf verwendbarer Radiumträger samt Intubator, Ztschr. f. Hals-, Nasen- u. Ohrenh. **31**:293-301, 1932.

9. Coutard, H.: Roentgen Therapy of Epitheliomas of the Tonsillar Region, Hypopharynx and Larynx from 1920 to 1926, Am. J. Roentgenol. **28**:313-331, 1932.

10. Howes, W. E., and Bernstein, L.: A System of Tumor Dosage, Records and Technique as Employed at the Brooklyn Cancer Institute, Am. J. Roentgenol. **50**:76-88, 1943.

11. Paterson, R.: The Radical X-Ray Treatment of the Carcinomata, Brit. J. Radiol. **9**:671-679, 1936.

received a so-called carcinogenic dose of roentgen therapy are living to date (February 1944).

The surviving patients who received roentgen therapy are listed in table 3 in the order of completion of their first cycle of treatment.

TABLE 3.—*Summary of Details of Roentgen Therapy for Ten Patients Who Are Living to Date*

Patient	Location of Lesion	Therapy		Duration, Days	Dose Delivered to Tumor, Roentgens
		Instituted	Completed		
J. S.	Intrinsic	9/ 7/37	10/ 2/37	25	6,200
W. P.	Intrinsic	3/23/38	4/23/38	31	6,050
I. Y.	Extrinsic	5/11/39	6/12/39	31	7,800
J. G.	Intrinsic	9/25/39	10/30/39	35	5,000
J. G.	Extrinsic	12/11/39	1/ 5/40	25	6,400
G. A.	Extrinsic	6/18/40	7/ 5/40	17	5,850
G. D.	Intrinsic	7/29/40	9/20/40	53	7,120
		10/27/41	11/17/41	21	2,070
		4/ 9/42	5/ 7/42	28	2,810
A. B.	Intrinsic	12/16/41	2/ 5/42	51	6,190
J. W.	Intrinsic	3/19/42	4/23/42	35	5,280
G. G.	Intrinsic	5/14/42	6/ 8/42	24	6,050

SUMMATION OF RESULTS OBTAINED

The end results for all types of treatment are recorded in table 4.

TABLE 4.—*Summarized Results of All Types of Treatment*

Therapeutic Procedure	Patients	Number Living	Average Survival Period, Mo.	Number Dead	Average Survival Period, Mo.
Fulguration and roentgen irradiation	3	1	38	2	10
Laryngofissure	8	4*	55	4†	63
Laryngectomy	5	2	47	3	37
Radiation, therapeutic	43	10	43	33	8
Radiation, palliative	11	0	0	11	4
No treatment	1	0	0	1	10
Total	71	17	46	54	13

* One who had proved recurrence of carcinoma following operation has survived to date of writing following roentgen therapy.

† One in this group died of intercurrent disease seven years after operation without evidence of recurrent carcinoma.

Surgical Treatment.—No type of surgical procedure resulted in cure in this series with carcinoma arising in the extrinsic larynx. Recurrence followed electrocoagulation in each instance. Epiglottic resection relieved the airway of a swollen edematous epiglottis and thereby appeared to have saved the life of 1 patient. Of 9 patients treated by laryngofissure, 5 are living. One of these received postoperative roentgen therapy for proved recurrence. Of 5 who were treated by laryngectomy, 2 are living and well three and four years after operation.

Surgical Treatment and Irradiation.—Recurrence followed electrocoagulation in every instance. Subsequent roentgen therapy resulted in the survival of 1 in 3. Two of the 9 patients subjected to laryngofissure received in addition roentgen therapy for recurrent tumor; 1 of these is living. Two of the patients treated by laryngectomy also received radiation in addition—1 radium, 1 roentgen rays. Neither of these survived.

Irradiation.—Ten of the 43 patients who were given a carcinogenic dose of roentgen radiation have survived to date of writing—a salvage of 23.25 per cent.

SUMMARY

Only carcinoma arising on the vocal cords (intrinsic) was observed to be amenable to surgical treatment in this series. Radiation therapy was shown to be of value in the treatment of both carcinoma arising on the cords and carcinoma of the extrinsic structures of the larynx. Of 68 men and 3 women with lesions proved to be carcinoma of the larynx who were admitted to the Brooklyn Cancer Institute from 1934 through 1942, 17 are living. Of the surviving patients, 13 had carcinoma originating in the intrinsic and 4 in the extrinsic larynx.

152 Clinton Street.

34 Plaza Street.

Case Reports

EXTRAMEDULLARY PLASMA CELL TUMOR OF THE MOUTH

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AND
MAJOR WRAY J. TOMLINSON
MEDICAL CORPS, ARMY OF THE UNITED STATES

In the most recent and comprehensive review of cases of extramedullary plasma cell tumor, Hellwig [1] found 65 cases reported in which the tumor occurred in the upper respiratory tract. Since his review, 1 case has been reported by McNamara and Rogers [2] in which the tumor occurred in a tonsil. Of the cases reported in which the upper respiratory tract was the site only 7 are recorded in medical journals having a general distribution among physicians specializing in diseases of the nose and throat in the United States. It is the purpose of this paper to report another case of extramedullary plasma cell tumor of the upper respiratory tract.

REPORT OF CASE

A 26 year old Salvadorian mestizo was admitted to the hospital complaining that for the past four and one half months he had suffered from nasal obstruction and frequent frontal headaches. The trouble began as pain in the mouth and throat which progressed to difficulty in nasal breathing in the four and one-half months. The nasal obstruction was so severe that he had difficulty in sleeping. The family history was noncontributory. The past history revealed that two years earlier the Caldwell-Luc operation had been performed for bilateral chronic maxillary sinusitis and that he had had gonorrhea three months prior to this admission. He denied having had any signs or symptoms of syphilis.

He was a well developed, well nourished mestizo, weighing 124 pounds (56.4 Kg.). The heart and the lungs revealed nothing of note. The blood pressure was 90 mm. of mercury systolic and 70 mm. of mercury diastolic. Routine laboratory tests, including Wassermann and Kahn tests of the blood and the spinal fluid, were negative. The urine showed no Bence Jones protein. A hemogram on admission revealed 3,830,000 erythrocytes per cubic millimeter with hemoglobin content 75 per cent (Tallqvist). The leukocyte count was 10,400 per cubic millimeter with polymorphonuclear neutrophils 82 per cent and lymphocytes 18 per cent. Thick and thin blood films revealed no plasmodia.

There was chronic hyperplastic rhinitis with crusting in both nostrils, as well as a purulent postnasal drip. The turbinates were bilaterally adherent to the nasal septum by dense fibrous bands, leaving no airway in the right nostril and 40 per cent of the normal airway in the left nostril. In the mouth (fig. 1) there was extensive ulceration, destroying the uvula and involving the soft palate, the tonsils and the tonsillar pillars. It had destroyed the major portion of the soft palate and extended to involve the tonsils and the tonsillar pillars. The ulcerated area measured 4.0 by 2.5 by 1.0 cm. Its edges were smooth, hard and gray-white. The base was firm and fibrous in appearance. The adjacent nonulcerated tissue was smooth and had a markedly dry mucosal surface. The entire lesion was moderately anesthetic and bled freely on manipulation. The larynx was normal. No palpable cervical node or other evidence of lymphadenopathy was present. The hard palate was not visualized satisfactorily in the roentgenogram. There was slight thickening of the lining membrane of the left antrum. The skull and the long bones showed no changes. Dark field examination of material from the lesions revealed no Treponema pallidum. Smears of the nose and mouth gave no evidence of leprosy, tuberculosis,

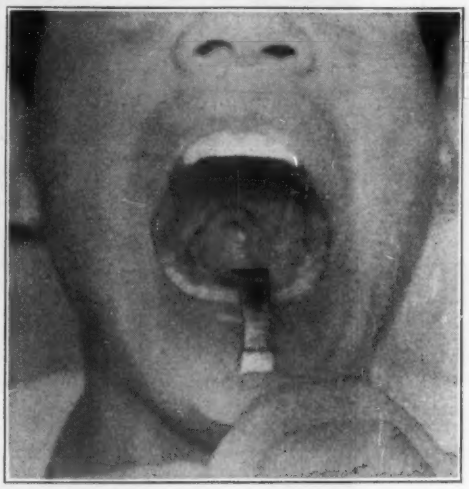

Fig. 1.—Ulceration of the soft palate with destruction of uvula as seen on admission.

From the Eye, Ear, Nose and Throat Service and the Board of Health Laboratory, Gorgas Hospital, Ancon, Canal Zone.

1. Hellwig, C. A.: Extramedullary Plasma Cell Tumors as Observed in Various Locations, Arch. Path. **36**:95-111 (July) 1943.

2. McNamara, W. L., and Rogers, R. J.: Extramedullary Plasma Cell Tumor of a Tonsil with Metastasis, Arch. Path. **36**:89-90 (July) 1943.

diphtheria or fusiform bacilli. The Frei and tuberculin tests gave negative results.

In a course of treatment lasting two months the patient was given a total of 0.59 Gm. of mapharsen intravenously and 1.37 Gm. of a bismuth compound intramuscularly. There was no response to this treatment. Local treatment of the nose readily cleared the discharge, and the septal adhesions were freed, relieving the difficulty in breathing.

Specimens were taken from six areas of the soft palate and pharynx for biopsy. Direct smears of the tissue were examined for tubercle bacilli, leishmanian bodies and Leishman-Donovan bodies, none of which were demonstrated. Histologic examination of the tissue revealed ulceration of the squamous epithelium in areas with a low grade inflammatory reaction in the denuded areas. In other regions the squamous epithelium was intact, showing only minor inflammatory

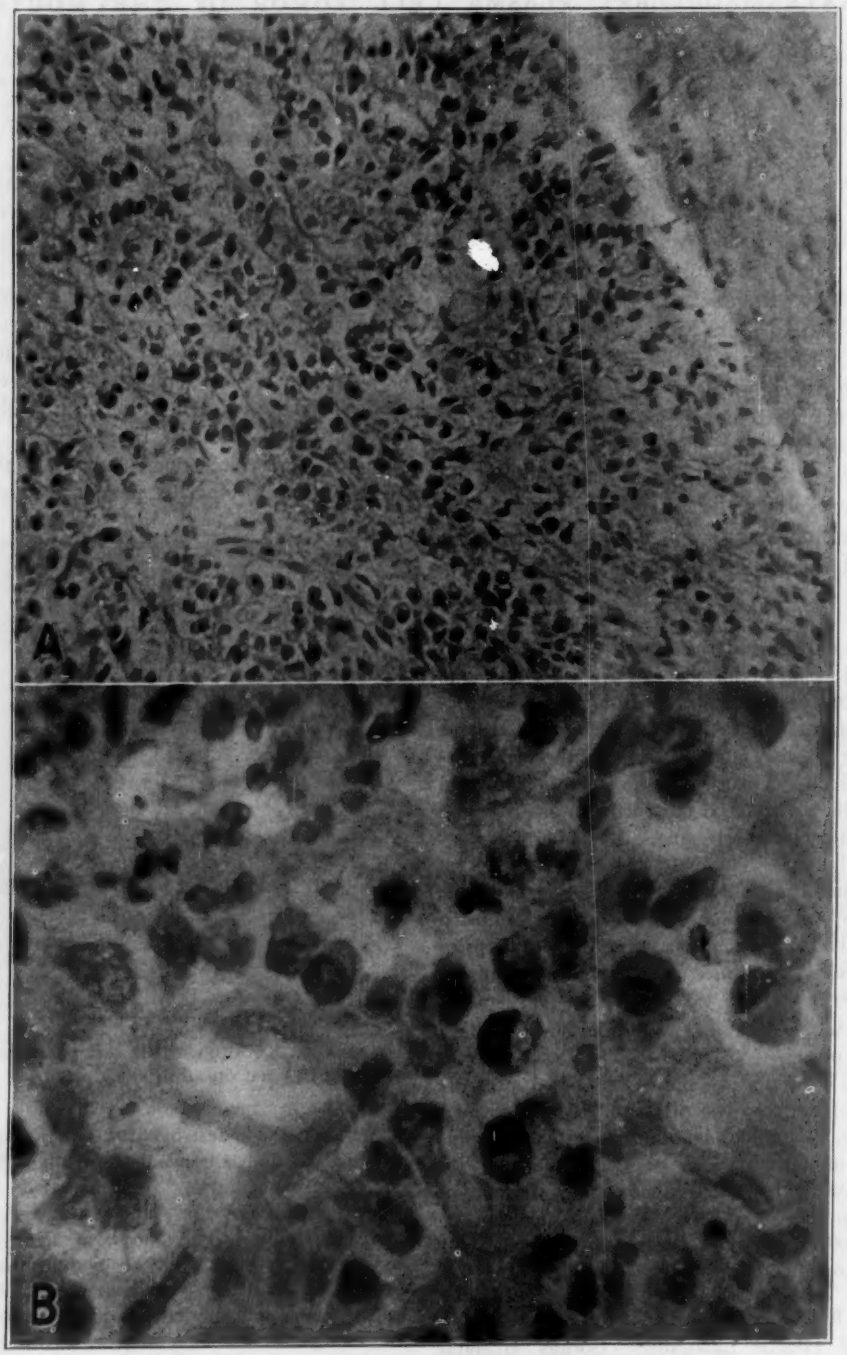

Fig. 2.—*A*, nodelike structures composed of plasma cells, raising the epithelium in the tumor. *B*, characteristic plasm cell type shown in high magnification.

hyperplasia. Beneath the epithelium were large node-like structures (fig. 2*A*), which in areas raised the epithelium. These structures were formed of reticulum containing enmeshed and attached plasma cells. The plasma cells (fig. 2*B*) were oval or round, varied from 10 to 12 microns in diameter and showed classic eccentrically placed cartwheel metachromatic nuclei, with unstained paranuclear regions in the basophilic cytoplasm. Occasional binucleated plasma cells were seen, but no atypical mitotic figures were encountered. No lymphoblasts were seen in the sections. Throughout the tumor mass were numerous capillaries, and the plasma cells in areas surrounded these capillaries. There was no necrosis of blood vessels. Peripherally from the lesions (fig. 3) the plasma cells and the reticular stroma extended gradually into the surrounding muscle and fibrous tissue. There were scattered foci of polymorphonuclear neutrophils and small lymphocytes in the regions surrounding the tumor areas. There was no histologic evidence of syphilis, tuberculosis, leprosy or leishmaniasis. The histologic diagnosis was extramedullary plasma cell tumor (plasmocytoma) of the mouth.

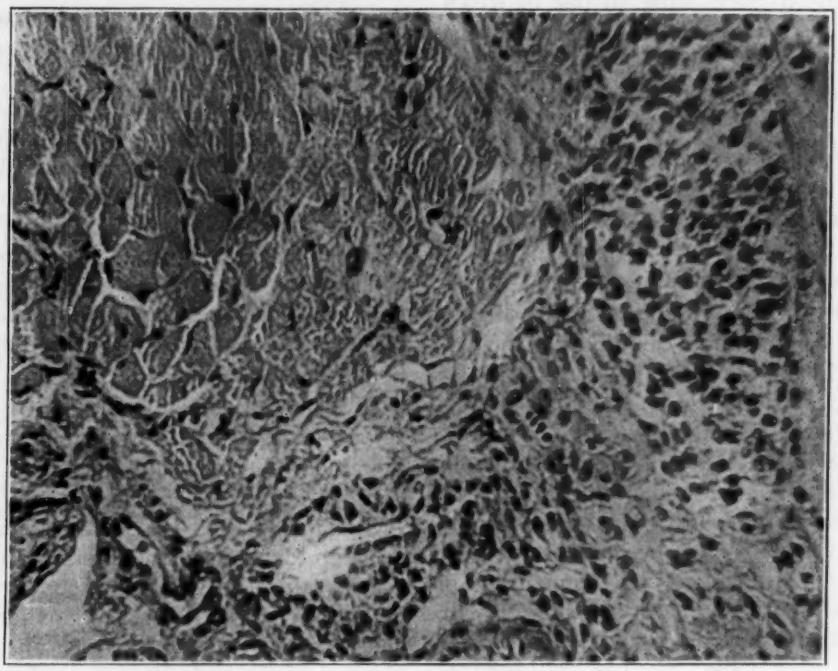

Fig. 3.—Extension of plasma cell tumor into adjacent muscle fibers.

Following the histologic examination, the lesions in the mouth and the nose were treated with roentgen rays. The treatment was given from February 25 to March 16 and from April 14 to May 7, 1943. It consisted of a daily dose of 100 to 150 roentgens in air given through two lateral cervical portals, each 10.0 by 10.0 cm. The factors were: 200 kilovolts (peak), 20 ma.; 50 cm. target skin distance; 0.5 mm. copper and 1.0 mm. aluminum for filtration. The total dose administered was 3,000 r in air to each portal.

The hyperplastic condition in the nose melted away dramatically, and the patient regained fairly normal-appearing nasal airways. The ulceration of the mouth did not respond as rapidly, but the lesions have regressed. Decrease in size occurred with smoothing of the edges, and epithelization occurred from the periphery. The central portion of the healed ulcer at the time of writing is sunken below the adjacent mucous membrane. There are small patches of redness throughout but no ulceration. The palatine remnant moves slightly on deglutition, appearing to be badly scarred. Seven months after the last roentgen treatment four small specimens were taken from the healed lesions for biopsy. Histologic examination revealed no evidence of tumor in these specimens. There was considerable scarring with fibrosis in the underlying stroma due to irradiation, with an intact but thin epithelial layer. The lesion has not extended further locally in the nine months following irradiation, and there is no evidence of involvement of lymph nodes. The patient has returned to his work as a laborer with pick and shovel and has had no further complaints.

SUMMARY

An extramedullary plasma cell tumor (plasmocytoma) of the mouth destroyed the uvula and part of the palate and involved the tonsils and tonsillar pillars in a young man, a Salvadorian mestizo. The lesion was grossly destructive and showed lateral extension but no anaplasia on microscopic examination. It was not suitable for excision; roentgen treatment stopped clinical extension and produced local regression with healing. There has been no extension or recurrence in the nine month period following the last treatment.

Progress in Otolaryngology

Summaries of the Bibliographic Material Available in the Field of Otolaryngology

TUMORS OF THE NOSE AND THE THROAT

GORDON B. NEW, M.D., AND EDWARD L. FOSS, M.D.
ROCHESTER, MINN.

Bowen's "precancerous dermatosis" is still considered by some authors as a precancerous dyskeratotic process but is regarded by the majority as a highly specialized form of superficial squamous cell epithelioma (carcinoma) with lateral intraepithelial spread. Brighton and Altman [1] present data on 2 typical cases of Bowen's disease of the mucous membrane, in one of which the anterior part of the nasal septum and in the other a vocal cord was involved, and on 4 cases of squamous cell epithelioma with intraepithelial spread. The relations between Bowen's disease and epithelioma of the mucous membrane resembling Bowen's disease are discussed, and it is pointed out that histologically the two lesions are closely related.

In a review of cancer of the face and mouth Blair and Byars [2] discuss the growth patterns of basal cell epithelioma (carcinoma), the advisability of biopsy and the general principles of treatment. In their opinion small lesions should be destroyed surgically. As squamous cell carcinoma of the skin of the face is a more rapidly developing disease than basal cell carcinoma and as it frequently metastasizes, more vigorous early treatment is needed than for the basal cell type. In general, the same rules of treatment apply as for the basal cell growth. Blair and Byars recommend that any black melanin-containing mole, whether subjected to chronic irritation or not, be removed. In their discussion of cancer of the lip they express the belief that any doubtful localized chronic change occurring on the vermilion or the mucocutaneous border of either lip should be regarded as squamous cell carcinoma until definitely proved not to be that. Methods of removal are discussed, and the indications for excision of lymph nodes of the neck are reviewed. Blair and Byars do not excise lymph nodes of the neck routinely in all cases of cancer of the lip. They advise excision of lymph nodes of the neck in those cases in which it is felt that danger of metastasis is present. This decision is made on the basis of the virulence of the growth as determined from clinical and microscopic examination, from the degree of extension of the growth and from the history of meddlesome or irritative treatment, if such has been given. In all cases of cancer of the tongue, cautery-biopsy is done, complete excision-biopsy being done when practical in cases of small lesions. Usually, whether the section proves the lesion to be cancer or whether the nature of the lesion remains doubtful, this is followed by interstitial implantation of a large dose of radon. Excision of lymph nodes of the neck should be considered in all cases of cancer of the tongue with the possible exception of those in which the lesion is extremely early and of low grade and those in which the initial lesion is almost surely hopeless.

The suggestion that degenerative and precancerous changes in the oral mucous membranes are among the important symptoms of deficiency disease is advanced by Martin and Koop.[3] Avitaminosis B is the greatest single cause of such precancerous oral lesions. In a review of the literature Martin and Koop have not found any reference to the role of avitaminosis B in the causation of oral cancer. The degenerative changes of the oral mucous membranes produced by a deficiency of the vitamin B complex are not peculiar to this condition but in many respects are identical in appearance with those produced by other forms of chronic irritation. Martin and Koop conclude that the most frequent and probably the most important form of chronic irritation from the standpoint of carcinogenesis in the oral mucous membranes is that due to avitaminosis B.

TUMORS OF THE NOSE AND ACCESSORY SINUSES

Data on 15 cases in which operation for dermoid cyst of the nose has been performed at the

From the Section on Laryngology, Oral and Plastic Surgery, Mayo Clinic.

1. Brighton, G. R., and Altman, F.: Bowen's Disease and Superficial Mucosal Epithelioma of Upper Respiratory and Alimentary Tracts, Arch. Otolaryng. **36**:354-371 (Sept.) 1942.

2. Blair, V. P., and Byars, L. T.: Cancer of the Face and Mouth, Texas State J. Med. **38**:641-645 (March) 1943.

3. Martin, H., and Koop, C. E.: The Precancerous Mouth Lesions of Avitaminosis B: Their Etiology, Response to Therapy and Relationship to Intraoral Cancer, Am. J. Surg. **57**:195-225 (Aug.) 1942.

Massachusetts Eye and Ear Infirmary in the last twenty years have been reviewed by Holmes.[4] Dermoid cyst of the nose usually starts in connection with either the nasal bones or the frontal bone, so that even if the cyst presents itself at the tip of the nose, its stalk of origin will be found to extend to, and be in contact with, either the nasal bones or the frontal bone. Three cases are presented, not as interesting cases, for most of them follow a common pattern, but as presenting operative problems.

Reports of intranasal encephalomeningocele are uncommon in the literature. McGillicuddy,[5] however, believes that it probably is diagnosed occasionally as nasal polyps or as fibroma. He suggests that in some of the cases in which meningitis and death have followed the removal of what seemed to be an innocent polyp the tumor may well have been an encephalomeningocele. If surgical intervention seems warranted, the question of the safest approach is debatable, but with use of sulfonamide compounds the prognosis is not hopeless. A case is reported in which a boy aged 13 years had a large intranasal encephalomeningocele. Operation was performed by the intranasal route. The patient did well for a year. Then meningitis developed, but with the aid of chemotherapy the patient recovered.

Davis [6] presents a case of nasal fibroglial heterotopia. The patient was an infant. The tumor was removed surgically. Death of the infant on the twenty-fifth postoperative day was caused by bronchopneumonia. After a review of the literature Davis concludes that tumors of this type belong to a group of congenital benign fibrogliomatous tumors which originate embryologically from encephaloceles.

TUMORS OF THE LIPS AND MOUTH

A discussion of the embryologic development of the structures of the floor of the mouth is given by Johnston.[7] He lists the cysts which are usually found in the floor of the mouth as dermoid, epidermoid, ranular, thyroglossal, mucous and branchial. After a discussion of their differential diagnosis Johnston concludes that even though the nature of a cyst of the floor of the mouth cannot always be recognized, an incorrect diagnosis is not a particular problem since any cyst in this site, regardless of its origin, has to be removed surgically.

Martin and Graves [8] report 2 cases of generalized neurofibromatosis in which there was bulky invasion of the oral cavity. Both of the patients were children. One of the oral tumors took on malignant, locally invasive characteristics and caused death.

A survey of the records of the State Institute for the Study of Malignant Diseases from Jan. 1, 1926, to Dec. 31, 1935 showed 636 consecutive cases in which cancer of the lip was treated by irradiation. In all of these cases the lesion was proved microscopically to be squamous cell carcinoma. Data on these cases are reviewed by Schreiner and Christy.[9] The patients were given roentgen therapy and radium therapy. Schreiner and Christy do not make any attempt to enter into a discussion of the comparative merits of surgical treatment and irradiation but urge that both methods be employed when indicated, in an attempt to improve the end results in cases in which there is metastasis. Of 27 patients who had lesions that were proved to be metastatic and were treated by implantation of radon seeds and radium needles and by irradiation with high voltage roentgen rays, only 2 (7.4 per cent) remained well five years or longer. Of 11 patients who had lesions that were proved to be metastatic and were treated with high voltage roentgen rays or radium pack alone, none survived.

In the discussion on treatment of cancer of the mouth Scarborough [10] states that irradiation is the method of choice in the treatment of the primary lesion. Excepted are pedunculated tumors occurring on the lip, buccal mucosa and anterior third of the tongue, as well as adenocarcinoma occurring on the roof of the mouth. These should be excised by cautery after preoperative irradiation.

Wilson [11] states that the eradication of the primary lesion of carcinoma of the lip may be accomplished in most cases by either surgical

4. Holmes, E. M.: Dermoid Cysts of the Nose, Ann. Otol., Rhin. & Laryng. **51**:662-670 (Sept.) 1942.

5. McGillicuddy, O. B.: Encephalomeningoceles in the Nasal Cavity, Ann. Otol., Rhin. & Laryng. **51**:516-525 (June) 1942.

6. Davis, E. W.: Gliomatous Tumors in Nasal Region, J. Neuropath. & Exper. Neurol. **1**:312-319 (July) 1942.

7. Johnston, W. H.: Cysts of the Floor of the Mouth, Ann. Otol., Rhin. & Laryng. **51**:917-930 (Dec.) 1942.

8. Martin, H., and Graves, C. L.: Plexiform Neurofibroma (von Recklinghausen's Disease) Invading the Oral Cavity, Am. J. Orthodontics **28**:694-702 (Dec.) 1942.

9. Schreiner, B. F., and Christy, C. J.: Results of Irradiation Treatment of Cancer of Lip: Analysis of 636 Cases from 1926 to 1936, Radiology **39**:293-297 (Sept.) 1942.

10. Scarborough, J. E.: Cancer of the Mouth, J. M. A. Georgia **31**:347-353 (Sept.) 1942.

11. Wilson, H.: Treatment of Carcinoma of Lip with Special Reference to Management of Regional Lymph Nodes, J. Tennessee M. A. **36**:140-144 (April) 1943.

means or irradiation. A block dissection of the regional lymph nodes increases the likelihood of a permanent cure. Follow-up observations should be made at frequent intervals and over a long period.

Because of the rarity of a metastasis in bone from epithelioma of the lip Tyler [12] reports data on 2 cases. One patient was a woman 33 years of age and the other a man aged 50 years.

TUMORS OF THE NASOPHARYNX

A simple method of irradiating the eustachian orifice with radium is presented by Emerson, Dowdy and Heatly.[13] The method gives excellent results in the treatment of deafness secondary to hypertrophy of lymphoid tissue about the eustachean orifices once the examiner has acquired the necessary experience in selecting cases by combining the data from the history, the audiogram and the nasopharyngoscopic examination.

In an effort to clarify some of the indications, contraindications and limitations of roentgen therapy of cancer of the nasopharynx, a review was undertaken of the clinical records of 63 patients, that is, all patients treated with roentgen radiation for cancer of the nasopharynx in the radiotherapy department of the Presbyterian Hospital and the Montefiore Hospital, New York, from 1926 to 1938. As a result of this review Lenz [14] concludes that at present roentgen therapy is the treatment of choice in cases of cancer of the nasopharynx. Various factors influence the prognosis. Among these are extent, location, invasion of bone, involvement of nerves and metastasis, as well as microscopic structure of the cancer. Roentgen therapy at 200 kilovolts as detailed here can control the cancer for five years or longer in about a fourth of all cases.

Needles, seeds or special applicators containing radium or radon may be employed within the nasopharynx, in addition to radiation from an external source. Unless the cancer is small and easily visualized, however, accurate placement of these intrapharyngeal sources of radiant energy to cover the entire growth is difficult. The cancerous process usually extends beyond the zone which the radioactive substance in the needles, seeds or applicators can effectively irradiate. This approach, therefore, is resorted to mainly after most of the growth has regressed under the influence of preceding roentgen therapy so that only smaller masses of cancerous tissue remain.

Eighty-five per cent of the nasopharyngeal tumors encountered in practice fall into the group of undifferentiated epithelioma, lymphoepithelioma, lymphosarcoma and plasmocytoma, which respond satisfactorily to doses of radiation which are well tolerated by the normal tissues. Martin [15] believes that irradiation is the treatment of choice in dealing with these tumors. Data on 4 cases are reported, and Martin discusses intracranial extension and involvement of lymph nodes.

TUMORS OF THE OROPHARYNX AND HYPOPHARYNX

Burman and Burman [16] define the Schmincke tumor as a malignant neoplasm of lymphoid tissue usually found in the pharyngeal region. This tumor is characterized by a peculiar admixture of lymphoid cell intimately associated with epithelial elements of an immature squamous or epidermoid type. There is a tendency to early and rapid metastasis, as the tumor is highly malignant. It is, however, extremely radiosensitive. Burman and Burman discuss the history, clinical manifestations, pathologic features and treatment of Schmincke's tumor. Three cases encountered in a period of six months are reported.

TUMORS OF THE LARYNX

The anatomy of the anterior commissure tendon is discussed by Broyles.[17] He concludes that in all probability early recurrence in cases of carcinoma of the anterior portion of the larynx should be considered continuation rather than recurrence and that carcinomatous growth was retained in this tendon or in its insertion into the thyroid cartilage. In those cases of carcinoma of the larynx in which the growth has invaded the tendon and perhaps the cartilage, it would seem advisable either to perform laryngectomy or to remove the midportion of the thyroid cartilage along with the diseased cord.

The most useful information which can be obtained by roentgenologic examination of the larynx is obtained by means of an apparatus which produces a cross-sectional view of the

12. Tyler, A. F.: Epithelioma of Lip Metastatic to Vertebra: Report of Two Cases, Am. J. Roentgenol. **48**:76-77 (July) 1942.

13. Emerson, E. B.; Dowdy, A. H., and Heatly, C. A.: Use of Radium in Treatment of Deafness by Irradiation, Arch. Otolaryng. **35**:845-852 (June) 1942.

14. Lenz, M.: Roentgen Therapy of Primary Cancer of Nasopharynx, Am. J. Roentgenol. **48**:816-832 (Dec.) 1942.

15. Martin, C. L.: Cancer of the Nasopharynx, Ann. Otol., Rhin. & Laryng. **52**:146-160 (March) 1943.

16. Burman, H. J., and Burman, D.: Schmincke Tumor: Lymphoepithelioma of the Nasopharynx, Arch. Otolaryng. **37**:835-844 (June) 1943.

17. Broyles, E. N.: The Anterior Commissure Tendon, Tr. Am. Laryng. A. **64**:251-255, 1942.

tissues at any determined depth. While it is called by various names the term accepted for this apparatus by the majority of roentgenologists is "laminagraph." It produces what is called a body-sectional roentgenogram. The principle and construction of the laminagraph are explained by Law.[18]

Medical interest in histoplasmosis (Darling) has been aroused recently by the increased number of reports published. These accounts indicate that this endemic disease has become more prevalent than it was or that it has existed unrecognized. The disease, though endemic, is not restricted in geographic distribution. Twenty-two male and 10 female patients have died; their ages ranged from 6 months to 69 years. Van Pernis, Benson and Holinger[19] report a case of laryngeal histoplasmosis. The patient was a man aged 63 years. Mirror examination of the larynx revealed a small polypoid tumor in the midportion of the phonating edge of the left true cord. The aryepiglottic folds and arytenoid cartilages were thickened and their laryngeal surfaces had a soft, slightly ulcerated mass extending across the entire posterior commissure. The lesion was red and was covered with a gray exudate. The movability of the cords was impaired. Direct examination of the larynx substantiated the findings of mirror examination. A microscopic diagnosis of histoplasmosis was made. The patient died approximately five months after this diagnosis had been made. Van Pernis and his associates present a good discussion of histoplasmosis and its symptoms and signs.

Dean[20] reports data on histoplasmosis occurring in the larynx of a man aged 41 years. He describes the epiglottis as being thick, nodular and pale. It was tilted so that indirect examination of the larynx was impossible. Direct examination showed the whole interior of the larynx to be white and nodular. The false and the true cords were involved to such an extent as to be entirely obliterated. The glottic chink was converted into an irregularly rounded tube. There was a daily rise of temperature of about 1 F. A presumptive diagnosis of keratosis of the larynx with carcinomatous change was made. By the aid of the Lynch suspension apparatus, most of the epiglottis was amputated and tracheotomy was performed. On microscopic study a diagnosis of histoplasmosis was made. Treatment of this condition has been of no avail.

It is axiomatic today that laryngeal tuberculosis is always secondary to a pulmonary focus. In a review of data on 1,800 patients observed at White Haven Sanitarium Donnelly[21] found that in 26 cases laryngeal symptoms developed before any systemic signs. In several of these cases there was moderately or far advanced pulmonary tuberculosis.

New[22] reports 2 cases in which a congenital laryngeal cyst was treated satisfactorily by lateral thyrotomy. The treatment of mucous cyst and hemorrhagic cyst is a matter of removing the tumor under suspension laryngoscopy. The treatment of congenital laryngeal cyst depends on the size and the extent of the cyst. The Lynch suspension apparatus may be employed in the care of the smaller ones. It is a more satisfactory procedure to remove a large cyst by lateral thyrotomy.

Gatewood[23] reports 2 cases in which chondroma of the larynx was treated successfully by laryngofissure. In a comprehensive article he explains that roentgen examination of a patient who has unexplained laryngeal symptoms may disclose early chondroma, whereas a lesion of soft tissue may not be visualized. Because of its insidious nature and slow growth, chondroma may exist undetected for years in the subglottic region of the larynx. The management of laryngeal chondroma depends on the location and the extent of the growth. When the lesion is extensive and invasive, total laryngectomy may be preferable. However, if possible, this procedure should be made a last resort, as it is better to give laryngofissure an opportunity even though there may be considerable doubt of its success, because chondroma is a type of lesion which will tolerate a secondary operation with little difficulty.

Iglauer[24] presents a case of myoblastoma of the larynx. The patient was a Negro woman aged 41 years. On mirror examination a large pedunculated tumor was seen in the posterior portion of the larynx between the arytenoid cartilages. It was globular and was the size of a hazelnut. Its surface was slightly corrugated,

18. Law, F. M.: Use of X-Rays in the Larynx, Tr. Am. Laryng. A. **64**:201-205, 1942.

19. Van Pernis, P. A.; Benson, M. E., and Holinger, P. H.: Laryngeal and Systemic Histoplasmosis (Darling), Ann. Int. Med. **18**:384-392 (March) 1943.

20. Dean, L. W., Jr.: Histoplasmosis of the Larynx, Tr. Am. Laryng. A. **64**:175-178, 1942.

21. Donnelly, J. C.: Pulmonary Tuberculosis Masquerading as Laryngitis, J. A. M. A. **120**:675-679 (Oct. 31) 1942.

22. New, G. B.: Treatment of Cysts of the Larynx, Arch. Otolaryng. **36**:687-690 (Nov.) 1942.

23. Gatewood, E. T.: Chondroma of the Larynx: Report of Two Cases Treated by Laryngofissure, Tr. Am. Laryng. A. **64**:238-250, 1942.

24. Iglauer, S.: Myoblastoma of the Larynx, Ann. Otol., Rhin. & Laryng. **51**:1089-1093 (Dec.) 1942.

and it was the color of butter. The mass moved upward during phonation, exposing the vocal cords, which were normal in appearance and in motion. The tumor was removed by direct laryngoscopy, and microscopic examination revealed myoblastoma. Eight cases of myoblastoma of the larynx have been reported in the literature.

A case of papilloma occurring in the larynx of a patient 40 years old is reported by Boies.[25] This condition had existed for thirty-five years, originating when the patient was 5 years old, and had not undergone basic change. Surgical treatment resulted in a cure. In a second case papilloma occurred in the trachea of an adult. The causation, the possible endocrine factor in papilloma of children and the question of a precancerous aspect of papilloma of adults are discussed.

An excellent discussion of carcinoma of the larynx is presented by LeJeune and Bayon.[26] In the first group of carefully selected cases in which carcinoma is confined to one small portion of the surface of one vocal cord the authors recommend suspension laryngoscopy. The second group includes those cases in which early cancer of the vocal cord is either too far advanced or too unsatisfactorily located for operation by intralaryngeal dissection but in which there is yet reasonable hope of cure without the necessity of total extirpation of the larynx. The ideal case is one in which the lesion involves the middle portion of a vocal cord with both ends uninvolved. Twenty cases in which thyrotomy had been performed are reported. In the third group are placed those cases in which the lesion, although considered too extensive for laryngofissure, is yet confined within the cartilaginous structures of the larynx. Lagging of the involved cord and certainly fixation of the cord are indications that the lesion is too far advanced for successful laryngofissure. Involvement of an entire cord or invasion across the anterior commissure with a considerable involvement of both cords is likewise a contraindication to laryngofissure. In the fourth group are placed those cases in which the lesion is too extensive for surgical treatment, the so-called extrinsic type of carcinoma. Usually little can be offered to the patient in these cases. Radiation therapy may prolong life but often the complications of such therapy only add to the misery already present. As far as cure is concerned, the hope is too forlorn to offer much in that direction.

Lenz [27] states that roentgen treatment is employed chiefly for three types of disease of the larynx: chronic inflammation, benign tumor and cancer. Tissue that is the site of inflammation is more sensitive to roentgen rays than the adjacent normal tissue, and the latter remains practically unaffected by the small doses of roentgen rays necessary to inhibit the growth of the former. Benign tumors do not respond to roentgen therapy as readily as tissue that is the site of inflammation, and some are so radioresistant as to make their treatment by roentgen rays impracticable. Carcinoma of the larynx is usually more radioresistant than either of the first two types of growth.

In a comprehensive review of the criteria of treatment for carcinoma of the larynx Jackson and Blady [28] list the indications for laryngofissure and laryngectomy as follows: 1. A lesion occupying the middle third of one vocal cord is suitable for laryngofissure and the "clipping" technic. 2. A lesion reaching the anterior commissure and even involving the opposite cord is also amenable to extirpation by the laryngofissure route, but in such cases the "anterior commissure" technic should be used. 3. A lesion in which the growth involves a vocal cord but has reached the posterior end of the cord and produced impairment of motility, or has extended subglottically, ordinarily calls for total laryngectomy. 4. A lesion which has invaded cartilage (but not muscles) also calls for laryngectomy provided there are no metastatic growths.

Lesions for which irradiation is indicated are listed as follows: 1. A lesion unsuitable for laryngofissure and for which laryngectomy is contraindicated by the age, the physical condition or the temperament of the patient. These factors rarely, if ever, contraindicate the less radical procedure of laryngofissure, but they are to be regarded as relative contraindications to laryngectomy. 2. An "inoperable" growth which is extrinsic by origin or extension or which has metastasized to the cervical lymph nodes. Such a neoplasm must be treated by protracted irradiation, followed immediately by implantation of radon, either through the skin or after surgical exposure. 3. A lesion which has reached

25. Boies, L. R.: Papilloma of the Larynx: A Report of Two Unusual Cases, Laryngoscope **53**:101-111 (Feb.) 1943.

26. LeJeune, F. E., and Bayon, P. J.: Cancer of Larynx, Ann. Otol., Rhin. & Laryng. **51**:460-470 (June) 1942.

27. Lenz, M.: X-Ray Treatment of Diseases of the Larynx, Ann. Otol., Rhin. & Laryng. **52**:85-108 (March) 1943.

28. Jackson, C. L., and Blady, J. V.: Criteria for the Selection of Treatment of Carcinoma of the Larynx, Arch. Otolaryng. **37**:672-679 (May) 1943.

the posterior extremity of the cord but has not impaired motility of the cord. Such growths constitute a group for which laryngofissure is contraindicated but for which irradiation may be preferred to laryngectomy. It is the consensus at present that impairment of motility contraindicates laryngofissure, and although such impairment is not a contraindication to irradiation, it is not a favorable sign. Complete fixation of one or both sides of the larynx, on the other hand, is considered even less favorable.

Roffo and Ferrari [29] believe that laryngectomy is the treatment of choice for extensive laryngeal lesions if there are no contraindications. Intralaryngeal carcinoma is best treated by laryngectomy because of localization of the lesion inside the cartilaginous shell. This is also true of carcinoma of the larynx with limited invasion of the neighboring structures. Adenopathy is a contraindication to the operation. Laryngectomy is performed only when there are no general contraindications, such as age, weakness, diabetes, nephritis, myocarditis and so forth. Roentgen therapy is resorted to only if contraindications to surgical intervention exist or if the patient refuses operation.

Lambert and Watson [30] devised a method of roentgen therapy which they believe is applicable to unilateral laryngeal carcinoma, provided cartilage is not involved and the growth does not extend in a vertical direction for more than 3 cm. The whole treatment is carried out in the operating theater, while the patient is under intratracheal anesthesia. A simple skin flap or a collar incision carried just across the midline may be found to be most convenient. After the overlying muscles have been stripped from the ala of the thyroid cartilage, the ala is skeletonized, and all of it is removed, care being taken to leave the internal layer of perichondrium intact. The larynx is now ready to be treated with the Chaoul "contact" x-ray tube. The wound is then closed without drainage, and the treatment is complete. This treatment has been used in 11 cases. There has not been sufficient lapse of time to enable Lambert and Watson to make any claim as to finality of results.

Patients who have advanced extrinsic laryngeal cancer present a distressing situation in which there is practically no hope of cure and in which conservative palliative procedures are usually of little avail. Pain is an outstanding complaint, difficulty with respiration is more or less constant unless there is a tracheotomy tube in place, and the sanguinopurulent discharges add to the general discomfort. In 5 cases of advanced extrinsic laryngeal carcinoma in which radiation therapy had been used but had failed to control the growth, Brunschwig [31] performed a radical surgical excision encompassing the gross limits of the tumor. While "cure" was not anticipated, the clinical course in the limited series was such as to justify the performance of his operation as a palliative measure, there having been no clinical or roentgenologic evidence of metastasis beyond the cervical region at operation.

Greene [32] discusses a new type of artificial voice box which has been developed recently by Gilbert Wright for the National Hospital for Speech Disorders. The instrument is completely external, is inconspicuous and precludes all possibility of infection or tracheotomic irritation.

Gatewood [33] discusses a simple method by which beginners may be instructed in the use of esophageal speech. He explains that the actual mechanism of esophageal speech is primarily dependent on the act of insufflating or swallowing air and using it under voluntary control in such a way that it is synchronized with sphincteric action of the esophagus situated near the hypopharynx. By persistent speech gymnastics, the esophageal constriction gradually approaches the function of a normal laryngeal glottis and finally acquires the ability to produce highly specialized tone vibrations.

TUMORS OF THE TRACHEA

Priest [34] presents data on tracheal ectasia occurring in a white adult man. Tracheal ectasia is reported under various other names: tracheal hernia, tracheocele, tracheal diverticulum, aerial goiter, aerocele and bronchocele.

Marshall and Cookson [35] report data on a tracheobronchial cyst occurring in a baby aged 7 months. This cyst was discovered at necropsy.

29. Roffo, A. H., and Ferrari, R.: Treatment of Cancer of the Larynx in the Institute of Experimental Medicine, J. Internat. Coll. Surgeons **5**:401-427 (Sept.-Oct.) 1942.

30. Lambert, V., and Watson, T. A.: Treatment of Carcinoma of Larynx by Chaoul "Contact" X-Rays: Preliminary Communication, J. Laryng. & Otol. **57**: 222-224 (April) 1942.

31. Brunschwig, A.: Panlaryngectomy for Advanced Carcinoma of the Larynx, Surg., Gynec. & Obst. **76**: 390-394 (April) 1943.

32. Greene, J. S.: Composite Postoperative Therapy for the Laryngectomized, Laryngoscope **53**:13-16 (Jan.) 1943.

33. Gatewood, E. T.: Development of Esophageal Speech After Laryngectomy, South. M. J. **36**:453-455 (June) 1943.

34. Priest, R. E.: Tracheal Ectasia with Report of Case, Ann. Otol., Rhin. & Laryng. **51**:1055-1061 (Dec.) 1942.

35. Marshall, P. C., and Cookson, H. A.: Tracheobronchial Cyst, Lancet **1**:305-306 (March 6) 1943.

TUMORS OF THE ESOPHAGUS

Sampson and Zelman [36] reviewed 25 cases of grossly pedunculated benign tumor of the esophagus. A case of pedunculated benign tumor is reported. The patient was a man aged 70 years. The polyp was extirpated through an esophageal speculum. After reviewing the cases the authors conclude that endoscopic removal appears to be the logical means of attack for the grossly pedunculated benign tumor.

A growth originating in the hypopharynx may involve the opening of the esophagus at an early stage and, conversely, a growth in the upper part of the esophagus may spread to the hypopharynx. Wookey [37] believes that there is no essential anatomic or histologic difference in structure between the esophagus and the pharynx and that tumors arising in these regions are identical in their pathologic characteristics and method of spread. The vast majority of these tumors are diagnosed as epidermoid carcinoma and are slow growing and relatively late in metastasizing. The method of spread is to neighboring lymph nodes. When distant metastatic growths occur, they usually are found in the advanced stages of the disease. Methods of removing growths involving the lower part of the pharynx and the upper part of the esophagus are described. Reports of 4 cases are used to illustrate the various methods of surgical removal.

Holinger and Hara [38] have made a study of 100 consecutive cases of carcinoma of the esophagus, 80 of which were observed in the Research and Educational Hospital of the University of Illinois prior to July 1942. There were approximately 137,000 admissions to the outpatient department during this period, or 1 patient suffering from cancer of the esophagus among every 1,712 newly admitted patients. Twenty additional cases were included from private sources, thus making a total of 100. Carcinoma of the esophagus is a highly malignant disease. Because of its insidious onset and relatively smooth course in its incipiency, no patient can establish its beginning definitely. The tumor remains localized until very late, and metastasis to distant organs is found in less than 40 per cent of the cases. Preexisting benign growth, scar, diverticulum, hiatal hernia, cardiospasm and ulcer are thought to be predisposing factors. Roentgenologic examination and esophagoscopy are the two most important procedures in establishing the diagnosis. Dysphagia is always intermittent in the beginning but is usually persistent as a late symptom. It is indicative of obstruction due to endoesophageal growth or infiltration of the wall of the esophagus, interfering with its normal function. Absence of demonstrable physical signs is the characteristic feature of the disease. An erroneous diagnosis of globus hystericus, cardiospasm or gastric ulcer is likely to be made in the early stages. No correlation between the patient's complaints and the extent of the lesion was found in this series. Surgical treatment offers the best opportunity for cure while the growth is still limited to the lumen of the esophagus.

In resection of the esophagus for carcinoma there are three different approaches and technical procedures, depending on the levels at which the lesions occur. Adams [39] states that each particular level has its special problems, and the technic of resection at that level is developed and made to meet these problems. These three surgical divisions of the esophagus are the cervical, the thoracic upper two thirds and the thoracic lower third. Resection of the esophagus at any level for carcinoma is a fairly well standardized procedure, and the methods of resection are described in detail in this paper.

Watson [40] gives a brief review of the history of surgical progress in the treatment of cancer of the cervical segment of the esophagus. He finds that carcinoma of the upper part of the esophagus is curable by radiation. Five cases are reported. In 1 case the involved portion of the esophagus was removed. Watson gives a detailed description of his plastic repair of this defect.

Past experiences with radiation in the treatment of carcinoma of the esophagus have been without encouragement. To a patient suffering from carcinoma of the esophagus, surgical treatment has afforded the one hope of cure. Any such lesion involving the proximal portion of the upper third of the esophagus is associated so intimately with the larynx, or involves it in such a manner, that both the esophagus and the larynx must be removed if cure is to be expected.

36. Sampson, P. C., and Zelman, J.: Pedunculated Tumors of Esophagus, Arch. Otolaryng. **36**:203-211 (Aug.) 1942.

37. Wookey, H.: The Surgical Treatment of Carcinoma of the Pharynx and Upper Esophagus, Surg., Gynec. & Obst. **75**:499-506 (Oct.) 1942.

38. Holinger, P. H., and Hara, H. J.: Cancer of the Esophagus: Study of One Hundred Consecutive Cases, Laryngoscope **52**:968-982 (Dec.) 1942.

39. Adams, H. D.: Carcinoma of the Esophagus, S. Clin. North America **22**:709-719 (June) 1942.

40. Watson, W. L.: Cancer of the Cervical Esophagus, Ann. Surg. **116**:86-97 (July) 1942.

Two cases of carcinoma of the proximal portion of the upper third of the esophagus are reported by Hudson.[41] These cases illustrate in a dramatic manner the value of complete removal of the carcinomatous lesion and the disappointment that can follow anything short of complete removal.

Smithers, Clarkson and Strong[42] believe that roentgen therapy has much to recommend it in the treatment of carcinoma of the esophagus, for it is the most effective method of securing palliation and at the same time causes the patient least discomfort.

41. Hudson, W. A.: Carcinoma of the Esophagus: Some Observations with Two Case Reports, Ann. Otol., Rhin. & Laryng. **51**:1125-1129 (Dec.) 1942.

42. Smithers, D. W.; Clarkson, J. R., and Strong, J. A.: The Roentgen Treatment of Cancer of the Esophagus, Am. J. Roentgenol. **49**:606-634 (May) 1943.

Book Reviews

The Otitic Perilymphatic Spaces (the Otitic Labyrinth). By Mario Rius, with the preface by Professor Juan Manuel Tato, adjunct professor in otorhinolaryngology, Faculty of Medicine of Buenos Aires, Argentina. Cloth. Pages 423, with 153 illustrations and 6 tables. Montevideo, Uruguay: Mosca Hermanos, 1943.

This is a concise, clear presentation embodying all of the present day concepts of the labyrinth. The presentation is thorough and excellent. The chapters on embryology and comparative anatomy are well written. The third chapter dealing with the microscopic aspects of the labyrinth contains a series of well drawn reproductions of sections of bone, uniquely presented, showing the intimate relations of all surrounding structures from different points of view. The chapter on physiology and physiopathology presents all the current opinions on the function of the labyrinth and the internal ear. The pathology is discussed from the standpoint of symptoms and prognosis, and this presentation is amplified by an excellent table of pathologic conditions, with their causes, microscopic features, symptoms and treatment. He deals in detail with both the medical and the surgical treatment of deafness, otosclerosis, Ménière's disease and generalized tinnitus. The typical operations on the labyrinth of Jansen and Frey-Hammerschlag and other modifications of the Hinsberg operation are discussed in great detail. Recent types of surgical treatment for vertigo are carefully described. Finally, the chapters on therapy deal with both medical and surgical procedures, incorporating under the latter the Wittmaack operation, Hughson's round window, the various operations of Holmgren Sourdille, Lempert, Ermiro de Lima, Shambaugh and finally the author's own modification. In conclusion, he presents a comprehensive report on sixteen operations with their results and the audiograms. All in all, this book presents an excellent summation of the entire subject. The type is excellent and easily read and the paper very fine. This book certainly merits an English translation.

Abstracts from Current Literature

Ear

GRADENIGO SYNDROME COMPLICATED BY PNEUMOCOCCIC MENINGITIS; RECOVERY AFTER INTENSIVE TREATMENT WITH PENICILLIN AND SULFADIAZINE. LEWELLYS F. BARKER, Am. J. M. Sc. **206**:701 (Dec.) 1943.

A woman aged 35 was admitted to the Johns Hopkins Hospital in a state of coma six days after pain developed in the right ear. The cerebrospinal fluid was cloudy and contained 3,300 cells. Culture of the fluid showed pneumococci. The day following admission there was complete paralysis of the muscles supplied by the right sixth and seventh nerves. Large doses of penicillin were given intravenously and intrathecally. Simple mastoidectomy was performed on the right side. Sodium sulfadiazine was given intravenously in doses sufficient to maintain the blood level of sulfadiazine between 11 and 17 mg. per hundred cubic centimeters. The patient recovered. Both penicillin and sulfadiazine were given in large doses. Barker states that sulfadiazine is the safest of the sulfonamide drugs.

DAVISON, Danville, Pa.

EFFECTS ON HEARING OF ACOUSTIC TRAUMA IN INDUSTRY AND WAR. SAMUEL L. FOX, South. M. J. **36**:97 (Feb.) 1943.

Fox states that noise as a cause of deafness was first established in 1886. There are three general types of traumatic or occupational deafness: (1) deafness caused by explosions, (2) deafness caused by chronic exposure to noise and (3) deafness caused by air pressure, or caisson deafness.

The first type follows an acute concussion of the inner ear with damage to the cochlea; the deafness is profound, permanent and of the nerve type. The second type results from long-continued exposure to loud noises; it is slowly progressive and permanent after its early stages. High frequency sounds are more destructive than low frequency sounds, and interrupted sounds produce more damage than continuous sounds of the same frequency. The third type occurs in patients who suffer rapid changes in atmospheric pressure, such as divers, aviators and mountaineers. Following such sudden changes in pressure, there is acute deafness, vertigo, faintness, vomiting, tinnitus and occasionally hemorrhage from the ear. The deafness is usually transient but becomes progressive and permanent if the occupation is persisted in without adequate protection.

The author believes that every employee subjected to excessive noise should be provided with a mechanical insulator to be worn in the ears, and that every prospective employee should have an audiometric test as a part of his routine physical examination.

SINGLETON, Dallas, Texas.

AN EVALUATION OF SOME EARLY OTOGENIC COMPLICATIONS. BURBANK WOODSON, South. M. J. **36**:486 (July) 1943.

Woodson reports 2 cases of acute fulminating otitis media complicated with pneumonia. One of the patients complained of severe pain in the ear, which was not relieved by paracentesis. The other patient had no pain referable to the ear or the mastoid process when first seen, but examination of the ear showed a markedly bulging drum membrane with obliteration of all landmarks; the drum membrane was incised, and this was followed by free bleeding, but no pus was obtained. Both patients were given large doses of sulfadiazine, and both made uneventful recoveries.

The author reports a third case in which the patient complained of recurrent prolonged attacks of middle ear infection with drainage and progressive loss of hearing. Bilateral mastoidectomy was performed to prevent further loss of hearing and to prevent intracranial complications. Sulfonamide compounds were not indicated and were not given in this case. The patient made an uneventful recovery.

SINGLETON, Dallas, Texas.

MONILIASIS OF THE EXTERNAL EAR CANAL. WILLIAM L. DOBES, South. M. J. **36**:614 (Sept.) 1943.

Dobes calls attention to the work that has been done and the progress made in attempts to separate and classify the saprophytic and the pathogenic fungi. The yeastlike fungi most frequently encountered are: (1) Monilia, (2) Cryptococcus and (3) Mycoderma. Monilia is subdivided into several strains, of which Monilia albicans is considered pathogenic, while the other strains are considered saprophytic. In reviewing the current literature the author found only two articles in which reference was made to involvement of the external canal by M. albicans. He reports a case of disease of the external canal due to M. albicans. The patient was treated with a 2 per cent solution of methylrosaniline chloride (gentian violet) at daily intervals, and the lesion was healed within ten days. Local applications of 1 per cent mercury bichloride in 50 per cent alcohol and of mercuric iodine in alcohol are sometimes used in treating this type of infection.

SINGLETON, Dallas, Texas.

A BACTERIOLOGIC, CLINICAL AND THERAPEUTIC STUDY OF ACUTE SUPPURATIVE OTITIS MEDIA IN INFANCY. A. AUGUSTO LATORRE and P. FRANCISCO LANDA, Rev. de otorrinolaring. **3**:63 (Sept.) 1943.

Latorre and Landa made a clinical study of acute suppurative otitis media in infancy. The bacteriologic analysis revealed the incidence of pathogenic microorganisms to be: Streptococcus haemolyticus 59.3 per cent, Staphylococcus 25 per cent, Pneumococcus 22.3 per cent and Pneumococcis type III 7.9 per cent.

In treatment they were extremely conservative, depending almost entirely on early paracentesis, irrigation and application of external heat. In this group no chemotherapy was employed. As to results, 78.3 per cent of the ears were cured without any complications; in 12.5 per cent the otitis became chronic; in 2.8 per cent symptoms referable to the mastoid process developed. Mastoidectomy was required in only 2 cases.

The authors stress the importance of early paracentesis, particularly in cases in which there is doubt as to the presence of a latent process. They also believe that small blood transfusions are of extreme value in

combating the infection. They depreciate the value of the use of sulfonamide compounds.

They studied a group of 45 cases in which sulfonamide compounds were employed and they had a control group of 50 cases in which the patients did not receive any chemotherapy. The results in each group were almost identical as to the duration of the discharge, the number of cases in which the otitis eventually became chronic and the number that ultimately required mastoidectomy. PERSKY, Philadelphia.

Pharynx

RECOGNITION AND RADIUM TREATMENT OF NASOPHARYNGEAL LYMPHOID TISSUE. GILBERT E. FISHER, South. M. J. **36**:702 (Oct.) 1943.

Fisher discusses briefly the effects of the treatment of lymphoid tissue with roentgen rays and radium. He then describes in detail the instrument used in treating nasopharyngeal lymphoid tissue and the method of application. He reports satisfactory clinical results in 234 of 250 patients treated. In conclusion he states: "Chronically infected and hypertrophied lymphoid tissue in the nasopharynx causes obstruction of the orifices of the eustachian tubes and is constantly covered with a thick tenacious discharge. Atrophic changes can be readily produced in this tissue by exposing it to the gamma rays of radium." SINGLETON, Dallas, Texas.

Larynx

CONCENTRATION RADIOTHERAPY OF CANCER OF THE LARYNX: A STUDY OF 413 CASES. MAX CUTLER, J. A. M. A. **124**:967 (April 1) 1944.

Cutler reports 413 consecutive cases of cancer of the larynx observed between January 1931 and January 1943. He discusses the question of extrinsic and intrinsic cancers, the surgical classification and the anatomic one. Many important points are brought out in his discussion. He reviews the classification used in the Curie Institute of Paris and continues with the relation between microscopic structure, prognosis and radiosensitivity.

A detailed description (with charts) is given on the method of concentration, and the results are commented on.

He concludes as follows: "Intrinsic squamous carcinoma of the larynx is curable by correct radiation therapy, the percentage of cures depending on the extent of the lesion and the efficiency of the treatment. Concentration radiotherapy has proved to be the most effective form of irradiation. When the cords are freely movable or only partly fixed, the curability is high; but when they are completely fixed, cure is difficult and rarely accomplished. Eighty-two per cent of the patients with movable and partly fixed lesions of the true cords are alive and have been free from disease more than three years. The voices of these patients are practically normal. The most significant result of this research is the eradication by means of an improved method of radiotherapy of a group of intrinsic squamous carcinomas of the larynx so advanced as to have required total laryngectomy and hitherto generally regarded as radioresistant and incurable by irradiation." GORDON, Philadelphia.

CANCER OF THE LARYNX. MURDOCK EQUEN, FRANK NEUFFER and WILLIAM B. MATTHEWS, South. M. J. **36**:321 (May) 1943.

The authors state that cancer of the larynx is on the increase. This is due to its earlier recognition and to the fact that more people are living to the cancer age. Hoarseness is the most frequent early symptom of laryngeal cancer, and any hoarseness that lasts more than three weeks should be regarded as due to cancer until proved not to be; it occurs in 95 per cent of cases, and often it is the only symptom for a number ot months.

Cancer of the larynx is most common in persons past 40 years of age, and its incidence increases up to 60 years of age. The diagnosis of the lesion is not difficult. Careful mirror and direct laryngoscopy will enable one to determine in most instances whether or not a new growth is present. If a lesion is present, a biopsy should be made to confirm the diagnosis.

The authors favor surgical treatment, and the extent of the surgical removal is governed by the extent and the location of the lesion. Frequently it is advantageous to supplement surgical treatment with irradiation of the involved regions. SINGLETON, Dallas, Texas.

DEVELOPMENT OF ESOPHAGEAL SPEECH AFTER LARYNGECTOMY. E. TRIBLE GATEWOOD, South. M. J. **36**: 453 (June) 1943.

Gatewood states that the surgeon's obligation to a laryngectomized patient does not terminate when the patient is discharged from the hospital. He must aid and encourage the patient to develop some form of communication and the esophageal voice is the means of choice. In the development of the esophageal voice persistent "speech gymnastics" are necessary, and many individual technics may be used by patients in developing this type of voice. The patient should be taught the fundamental methods of obtaining air in the esophagus and hypophyarynx and its control in association with the formation of letters, syllables, words and sentences. The instruction should begin within six to eight weeks after the operation, thus preventing the adoption of faulty methods of sound production, which are often difficult to discard.

SINGLETON, Dallas, Texas.

CARCINOMA OF THE ESOPHAGUS. FLETCHER D. WOODWARD, South. M. J. **36**:590 (Aug.) 1943.

Woodward states that carcinoma occurs more frequently than any other type of tumor of the esophagus. It occurs most often in men in the fourth and fifth decades of life. The ratio of its occurrence in men and women is given as from 4-5 to 1. The most frequent site of occurrence in men is the lower third; in women, the upper third. In the great majority of the cases it is squamous cell in origin; in an occasional case it is basal cell carcinoma or adenocarcinoma. The latter type tends to occur in the upper and lower portions because these are the gland-bearing parts of the esophagus. The tumor usually presents as intraesophageal masses, which may be ulcerative, nodular, polypoid or cauliflower-like. Dysphagia is an early symptom. As the growth develops, other symptoms occur, depending on the nature and the location of the lesion; bleeding, regurgitation or increasing difficulty in swallowing may be the most prominent. The diagnosis is best made

by careful roentgenologic, fluoroscopic and esophagoscopic studies. If the diagnosis is made early, surgical removal of the lesion is the most satisfactory treatment. Best results are obtained in cancer of the lower end of the esophagus. Radiation therapy is occasionally advised for its palliative effect.

SINGLETON, Dallas, Texas.

Nose

AIR-BORNE CROSS-INFECTION IN THE CASE OF THE COMMON COLD: A FURTHER CLINICAL STUDY OF THE USE OF GLYCOL VAPORS FOR AIR STERILIZATION. T. N. HARRIS and JOSEPH STOKES JR., Am. J. M. Sc. **206**:631 (Nov.) 1943.

Propylene glycol was vaporized to bactericidal concentration in wards of a children's convalescent home. The incidence of infections of the upper respiratory tract in these wards was compared with that in control wards and found to be much lower. The fact that the great majority of the infections of the upper respiratory tract in the control wards were common colds provides additional evidence of the virucidal effect of propylene glycol vapor and may give indirect evidence of the airborne transmission of the common cold.

DAVISON, Danville, Pa.

CARCINOMA OF THE NASOPHARYNX. CHARLES M. THOMPSON and ELMER R. GRIMES, Am. J. M. Sc. **207**:342 (March) 1944.

Thompson and Grimes present an analysis of 17 cases and point out that late diagnosis is one of the factors responsible for poor therapeutic results. They point out that any of the following signs or symptoms should lead to a thorough examination of the nasopharynx.

1. Enlargement of cervical lymph nodes.
2. Nasal obstruction or discharge or epistaxis.
3. Paralysis of one or more cranial nerves. Involvement of the fifth nerve causes facial pain. Involvement of the sixth nerve causes diplopia. Involvement of the ninth nerve causes dysphagia.
4. Headache due to direct extension of the tumor into the middle fossa.
5. Horner's syndrome.
6. Unilateral deafness and tinnitus.

The average duration of symptoms before the diagnosis was made was fifteen months. Treatment should always be preceded by biopsy. Intensive irradiation up to the limit of tolerance is the treatment of choice. The practice of irradiating enlarged cervical lymph nodes without careful examination of the nasopharynx is to be condemned.

DAVISON, Danville, Pa.

Society Transactions

CHICAGO LARYNGOLOGICAL AND OTOLOGICAL SOCIETY

SAMUEL J. PEARLMAN, M.D., *President*

WALTER H. THEOBALD, M.D., *Secretary*

Regular Monthly Meeting Dec. 6, 1943

Terminal Stages in the Development of the Human Stapes. Presented by BARRY J. ANSON, PH.D., EARL W. CAULDWELL, M.S., and ARTHUR F. REIMANN.

This paper will be published in full in the ARCHIVES OF OTOLARYNGOLOGY.

Muscular Variation of the Pharyngoesophageal Segment. Presented by DR. NORA B. BRANDENBURG.

The pharyngoesophageal segment was studied in 41 bodies. Attention was directed to the muscular coat surrounding the esophagus, especially to the so-called esophageal triangle located below the cricopharyngeal muscle. Separation between the pharynx and the prevertebral muscles was easily accomplished in all cases.

The majority of the fibers of the constrictor pharyngis inferior muscle were seen to ascend obliquely and insert into the median raphe. The most inferior fibers coursed horizontally and overlapped the beginning of the esophagus. The direction of their arrangement was directly opposite to that of the fibers of the pharyngeal muscles. Variations occurring in these structures result in marked variations in the muscular protection of the pharyngoesophageal segment.

Hernias in general bear a direct relation to integrity of tissue and muscular protection. With muscular variations there is an additional factor contributing to formation of hernias. A correlation of the muscular variations and deficiencies to different types of hernias in other regions has been established. It is believed that pulsion diverticulum of the esophagus bears the same direct relation to congenital muscular variations of the pharyngoesophageal segment and variations in Laimer's triangle as does inguinal hernia to the triangle of Hesselbach. There may be not only a variation in the number of muscle fibers attaching into the tendon of Gillette but a variation in the distribution, the quality and the number of muscle fibers diverging over the posterior surface of the esophagus. This diversity results in alterations of size, shape and configuration of Laimer's triangle, thus making it a vulnerable point for herniation.

DISCUSSION

DR. GLENN J. GREENWOOD: Dr. Brandenburg is to be congratulated on this interesting work. It was my privilege to read the manuscript. I wonder what the relative percentage of the variations was found to be.

In 1939 I saw a patient with acute diffuse suppurative mediastinitis secondary to traumatic rupture of a diverticulum of the cervical segment of the esophagus. The mediastinitis went on to a fatal termination in thirteen days. Of interest is the pathologist's report on the esophagus, to the effect that "on the right lateral wall just a little below the level of the cricoid cartilage there is a diverticulum 1 cm. in diameter and 1 cm. long. Its thin, white floor contains a small perforation." Dr. Brandenburg's described muscular variations of the pharyngoesophageal segment present a hypothesis which might help to explain the position of this pouch.

DR. PAUL HOLINGER: The problem presented in Dr. Brandenburg's thesis is not only of academic but of practical importance. Otolaryngologists know that clinically most diverticula occur to the left. I should like to ask her the percentage in which the muscular dehiscence was found on the left. Practically, of course, the observations reported explain the lodgment of foreign bodies in this area, the dehiscence accounting for the ease of perforation of the upper part of the esophagus. One acquires a great deal of respect for this area in viewing the complete absence of musculature in the upper portion of the esophagus as shown in Dr. Brandenburg's illustrations. One wonders why perforations do not occur more frequently in this locality when one sees the large portion of the esophageal ring covered only with mucosa.

I enjoyed the paper and I think Dr. Brandenburg is to be congratulated; the society, too, is to be congratulated on the acceptance of this candidate who has presented such an excellent paper.

DR. ALFRED LEWY: Has Dr. Brandenburg any information as to the possibility of local factors causing spasm of the cricopharyngeal muscle in addition to the ones she described?

DR. THOMAS C. GALLOWAY: This is a fine piece of work; it has been carefully performed and should be valuable.

In surgical correction of a diverticulum of the esophagus the important thing is the straightening of the angle where the diverticulum meets the main portion of the esophagus so one can really lift the esophageal pouch upward and straighten it out to form a nearly straight line with the descending esophageal wall. It has been generally assumed that the diverticulum begins above the cricopharyngeal muscle and hangs over that as a shelf, and if there has been inflammation in the diverticular sac there are adhesions of that angle. The difficult part of surgical removal of a diverticulum, whether in one or two stages, is the freeing of the angle. I think it important to have established just where the pathologic process starts, whether above or below the cricopharyngeal junction. If a diverticulum comes from any defective part of the upper portion of the esophagus, with herniation involving the mucosa and submucosa, the dissection is probably much less safe than has been assumed. I shall approach that angle in dissection with considerably more trepidation than heretofore.

DR. NORA B. BRANDENBURG: Dr. Greenwood asked the percentage of the triangular variations seen in my specimens. The specimens varied as much as did the noses of the 41 bodies examined. The triangles in most of the specimens were of different measurements. Only the gross anomalies were shown in my paper. In order to make a definite percentage of those to the right or

those to the left, I should have to establish a basic triangle, which I was unable to do. The largest triangle was 1.5 cm. across the base and 6 cm. on each side.

Dr. Holinger asked about the variations of the triangles to the left. I have no data on that, but I do not think it bears much relation to the fact that diverticular sacs are found most often on the left.

In answer to Dr. Lewy's question whether this research would explain the Plummer-Vinson syndrome, there are no factors in my research problem that would explain this syndrome.

SAMUEL J. PEARLMAN, M.D., *President*

WALTER H. THEOBALD, M.D., *Secretary*

Regular Monthly Meeting, Feb. 7, 1944

Laryngeal Management of Bulbar Poliomyelitis.
Presented by DR. THOMAS C. GALLOWAY.

In discussions of the respiratory difficulty in acute poliomyelitis, emphasis has been placed on central factors. Little attention has been paid to what happens in the peripheral respiratory tract.

In cases of bulbar poliomyelitis accumulated salivary and other secretions amounting to 1,500 to 2,000 cc. per day may lie as a pool over or in the airway, as has been seen by direct laryngoscopy, and may impede or prevent inflow of air, with production of serious anoxia. Or this collected fluid may be drawn forcibly into the lungs, especially if a respirator is used, producing asphyxia, obstruction and such sequelae as atelectasis and pneumonitis. Or this secretion may produce serious derangements of the coordination and rhythm of respiration, some of which are probably reflex since they occur in unconscious patients and are relieved when the secretion is removed.

Anoxia is probably important and seems to account for restlessness, depression and other symptoms, sometimes ascribed to the infection itself, since these are strikingly relieved when anoxia is corrected.

Most patients with poliomyelitis of the bulbar type will recover if treated early with oxygen, postural drainage, aspiration of secretions and parenteral administration of fluids, and with the respirator if needed. Two patients are cited, however, who were saved only by tracheotomy which prevented immediate asphyxiation, short-circuited secretion and allowed its aspiration, and relieved serious anoxia. The respirator was very satisfactorily employed with one of these after tracheotomy. This measure may well be more widely used before a critical stage is reached and should considerably lower the mortality from this disease (Galloway, T. C.: Tracheotomy in Bulbar Poliomyelitis, *J. A. M. A.* **123**:1097-1098 [Dec. 25] 1943).

DISCUSSION

DR. ALFRED LEWY: I think that the presentation is historic. I am not familiar with the literature on the subject, and I do not know whether or not Dr. Galloway is the first to offer the suggestion, but this is the first I have heard of it. The idea that the chief complication in poliomyelitis of the bulbar type is due to anoxia is important. Physicians often lose sight of the fact that all deaths are due to lack of oxygen consequent to circulatory or respiratory failure and that their first effort should be to get oxygen to that part of the system that needs it. Vital centers do not live long without oxygen.

Some years ago I advanced a method of draining the lung involved in pulmonary abscess by passing a catheter through the Mosher life saver which has had an opening made in the bottom. This can be passed down into the right or the left bronchus. It seems to me that this technic might be used pending tracheotomy in such cases as Dr. Galloway described.

DR. FREDERICK HILLER: I am sure all have been impressed by this contribution to the treatment of infantile paralysis. I myself have seen the life-saving effect of tracheotomy in a patient. There is no doubt that tracheotomy is indicated in certain cases of respiratory paralysis, those in which there is obvious obstruction of the air passage or disturbance of the physiologic separation of breathing and swallowing. Both indications may become urgent for a patient in a respirator, more so than for one outside it.

Obstruction of the air passage may occur in spinal as well as in bulbar paralysis, in the former because of motor inability to expectorate, in the latter because of disturbance of the cough reflex. The effect of passive respiration under negative pressure can be unfortunate in both types of obstruction. Harper and Tennant noted ten years ago that "the forced sucking in of air often caused aspiration of material from the throat and at the same time overcame the reflex coughing and choking by which such material is usually ejected." Even if one restricts the use of the respirator entirely to the treatment of spinal respiratory paralysis, the danger of aspiration followed by pneumonia remains. In Landon's well known statistics, based on 2,402 cases of poliomyelitis in 1931, 16 of 35 respirator-treated patients died within eighteen months from respiratory infections, chiefly pneumonia. Should paresis due to involvement of the vagus and glossopharyngeal nerves be added to the difficulties of respiration, the danger of aspiration becomes much greater. "The accumulation of secretion and food around the glottis may produce a rapid shallow type of breathing closely simulating intercostal paralysis" (J. L. Wilson). Paralysis due to involvement of the vagus nerve and the action of the respirator combine in abolishing the cough reflex and advancing the accumulation of large amounts of fluid in pharynx and larynx, which interferes gravely with respiration.

All who have had experience with the treatment of respiratory failure will agree that the differentiation of the spinal from the bulbar type is not always as simple as the textbooks would have one believe. Ascending paralysis may appear to be of the spinal type in the beginning, only to be more of the bulbar type after a day or so. No one would take a patient with such a history out of the respirator; one feels that he must be kept breathing to keep him alive. But breathing with aspiration from the pharynx means serious pulmonary complications, and insufficient respiration through an obstructed air passage means steadily increasing anoxemia. Anoxia of the tissues shows itself in impaired function of the brain as a whole, particularly in drowsiness progressing to coma; there is also a detrimental effect on the already depressed action of the respiratory center. Organic lesions in the gray and especially in the white matter of the central nervous system at autopsy should always be regarded as possible effects of anoxia when the well known symptoms of true inflammation are absent. There seems to be little doubt that many of the so-called encephalitic symptoms,

as well as manifestations of lesions of the pyramidal tract, are due to anoxia of tissues and not to localization of the poliomyelitic process.

Oxygen must be supplied to the tissues in such cases, and tracheotomy should be considered. If there is a chance that oxygenation of the blood may save the patient's life, tracheotomy may do so. The patient will regain consciousness, and the damaging effects of anoxemia on the respiratory center will be overcome. Tracheotomy will fail in the cases of severe bulbar poliomyelitis, in which the patient dies from combined respiratory and circulatory failure. We know that in cases of drowning or electric shock the heart will continue to beat for several minutes after respiration has ceased. In bulbar poliomyelitis, a heart that has been beating strongly, regularly and slowly under the effect of oxygen stimulation will fail rapidly under the combined effects of anoxemia and the inflammatory lesion of the circulatory center. This has been shown in animal experimentation; when the nerves to the carotid sinus and the aorta have been severed, thereby eliminating a great part of the nervous control of the circulation, the animal will die with a loss of only one tenth of its blood. The abolition of function of the medullary, circulatory and respiratory centers is, of course, a much more severe shock to the maintenance of circulation than the cutting of the buffer nerves, and the amount of blood withdrawn from the circulation by the peripheral loss of vascular tone exceeds by far the 10 per cent loss which will kill the experimental animal.

I do not think that bulbar respiratory disturbance per se is a contraindication to artificial respiration, provided the air passages have been kept free. At least one of Dr. Galloway's cases proves this point. Oxygen may help over a critical situation.

Dr. Thomas C. Galloway: Dr. Hiller was of great assistance in these cases. I wish there were time for him to discuss the histologic picture in poliomyelitis and especially the damage to brain and heart tissue from anoxia as contrasted with that from the virus infection.

Dr. Lewy's remarks were very kind. I think his idea of the Mosher life saver for aspiration might be valuable in these cases.

The So-Called Crypt System of the Human Pharyngeal Tonsil: A Study of Its Development, Adult Structure and Relations. Presented by Dr. L. B. Arey, of the department of anatomy, Northwestern University Medical School.

A difference of opinion exists concerning the structure and form of the pharyngeal tonsil. Many writers hold that the palatine, lingual and pharyngeal tonsils are all essentially alike in structure. Others stress the peculiar mucosal folding in the pharyngeal tonsils but deny crypts to it. However, up to the present time the exact morphologic character of the pharyngeal tonsil has not been determined through the method of reconstruction, as have that of the palatine tonsil (Minear, Arey and Milton) and that of the lingual tonsil (Hellman).

A pharyngeal tonsil of a newborn infant has been studied and reconstructed. A distinctive feature is the folding of the mucosa into roughly parallel ridges and troughs. Also prominent are the numerous pores that open from the free surface of the ridges and troughs into relatively large and long epithelial funnels. The latter are embedded in lymphoid tissue. These unbranching funnels resemble somewhat the simplest crypts of the palatine tonsil, but, unlike the palatine tonsillar crypts, each usually communicates with subtonsillar glands. Closer is the resemblance to the simple pits of the lingual glands, which do have glands opening from their depths. It might be argued whether the funnels of the pharyngeal tonsil are the dilated ducts of glands or whether they are simple crypts that have budded off glands. In either case the morphologic appearance and the lymphoid relationship are cryptlike in the accepted tonsillar sense.

DISCUSSION

Dr. Walter Theobald: Emerson said: "When you build a mousetrap, build the best mousetrap and the world will wear a beaten path to your door." I rise to compliment Dr. Arey on the tremendous study this brilliant presentation represents. The subject of tonsils is several hundred years old, but one can still enjoy new studies such as those so well shown here. I should like to have some clarification on one matter. Dr. Arey did not say much about the capsule, and rightly so, because he was talking about crypts. I remember that Dr. Eikelson asked: Has the tonsil a capsule or is it a fascia? In the operating room the experts talk about the capsule when removing tonsils. I wonder if he can tell us whether he considers it a capsule or an aponeurosis.

Dr. L. B. Arey: I think the answer to Dr. Theobald's question depends on definition. What is a capsule? I see no reason why a capsule cannot be a fascia. What is the capsule of the thyroid? It is part of the cervical fascia; it is a region where a gland has developed, has enlarged and has pressed on and compressed the tissue around it. As a result, the compressed tissue has been forced to consolidate into a capsule. Looking at the stages of development of a palatine tonsil, one will be again impressed by the fact that as the tissue gets bigger it presses on the underlying fascia; the result is that the so-called capsule of the tonsil is nothing but a fascial region that has been subject to pressure. I do not see any reason why one should question the propriety of a capsule developing in that way. From such a capsule in the palatine tonsil there is connective tissue which extends inward between the folds of lymphoid tissue and flattens into the septums or trabeculae of the tonsil. I do not look on it as unorthodox to have capsules and trabeculae develop in that way or feel that one should apologize in speaking of such an origin for these structures.

There is one point I failed to mention in my talk. Many workers have reported the presence of cystic epithelial structures in the pharyngeal tonsil. They have been reported as being pathologic things, which they are, but related to ducts. What is the genesis of such cystic cavities? The point which I think has been missed is that the whole process of dilatation is already there from early embryologic life. The actual facts and findings of cysts are well known, but the thing that has not been known is that the forerunner of the cyst is the dilated duct which is a morphologic structure, perfectly normal from the early months onward.

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